Paul

Access DB# 76618

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: P Spivack Examiner #: 70400 Date: 9/23/02
Art Unit: 1614 Phone Number 30 8 4703 Serial Number: 10/002526
Mail Box and Bldg/Room Location: 2D05 Results Format Preferred (circle): PAPER DISK E-MAIL
2D01

If mor than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

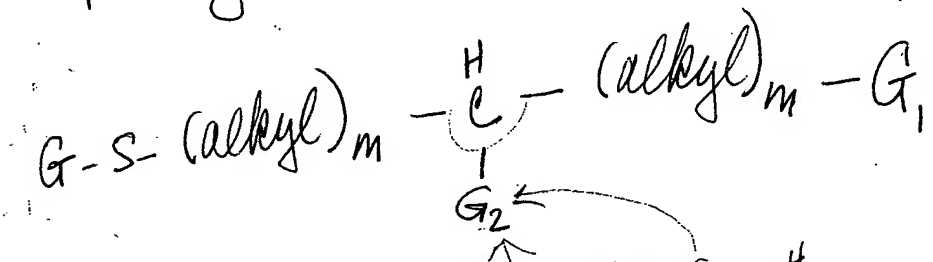
Title of Invention: Tx Radiation Exposure

Inventors (please provide full names): Hausheer, Frederick

Earliest Priority Filing Date: 10/26/01

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Please search methods of treating radiation exposu comprising administering a compound of



m = 0-5, but if either nor m = 0, then G2 = H

G = H, alkyl, methionine, cysteine, cystine or -S-(alkyl)m-C- (G2)

G1 = $SO_3^- M^+$, $PO_3^{2-} M_2^{2+}$, $PO_2S^{2-} Mg^{2+}$

M = H or an alkali metal ion

G2 = H, -OH, -SH, but if G = H, then G2 is not -SH

Thank

****

STAFF USE ONLY	Type of Search		Vendors and cost where applicable	
Searcher:	POINT OF CONTACT: PAUL SCHULWITZ	NA Sequence (#)		STN 302.55
Searcher Phone #:	TECHNICAL INFO. SPECIALIST	AA Sequence (#)		Dialog
Searcher Location:	CM1 6B06 TEL. (703) 305-1954	Structure (#)	2	Questel/Orbit
Date Searcher Picked Up:		Bibliographic		Dr.Link
Date Completed:	9/25	Litigation		Lexis/Nexis
Searcher Prep & Review Time:	9/27 60	Fulltext		Sequence Systems
Clerical Prep Time:		Patent Family		WWW/Internet
Online Time:	27	Other		Other (specify)

PTO-1590 (8-01)

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L1                STR
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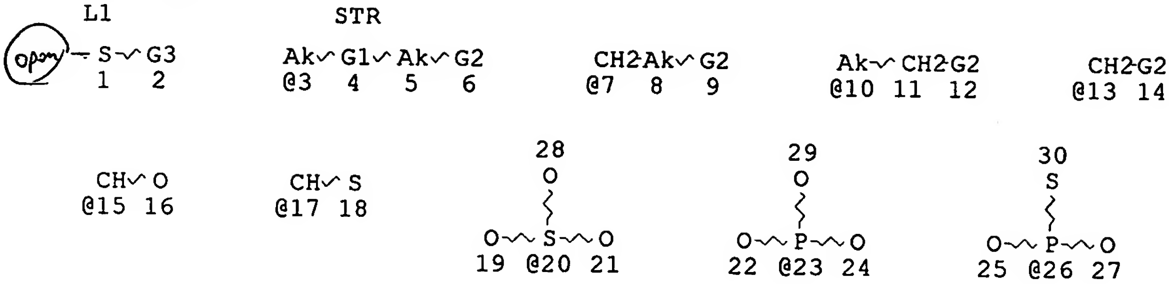


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VAR G2=20/23/26
VAR G3=3/7/10/13
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CONNECT IS E2   RC AT    5
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CONNECT IS E1   RC AT   16
CONNECT IS E1   RC AT   18
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS   30

STEREO ATTRIBUTES: NONE
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                 P/ELS AND O>1) OR (S/ELS AND P/ELS AND O>2)
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L13         1376 SEA FILE=REGISTRY SUB=L4 SSS FUL L1
L14          159 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L13 (L)(THU OR BAC OR DMA OR
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L20            4 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L14 AND RADIATION
L21         4545 SEA FILE=HCAPLUS ABB=ON  PLU=ON  RADIOPROTECTANTS+OLD/CT
L22            2 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L21 AND L13
L25            5 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L22 OR L20
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G not defined in search in order to get broader number of substances.

5 Hits mention radiation or ~~[crossed out]~~ radioprotective agents

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=> d ibib abs hitstr hitind 1-5
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L25 ANSWER 1 OF 5 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER:	2000:115117 HCAPLUS
DOCUMENT NUMBER:	132:273979
TITLE:	Ras-Related GTPase RhoB Forces Alkylation-Induced Apoptotic Cell Death
AUTHOR(S):	Fritz, Gerhard; Kaina, Bernd
CORPORATE SOURCE:	Division of Applied Toxicology, Institute of Toxicology, University of Mainz, Mainz, D-55131, Germany
SOURCE:	Biochemical and Biophysical Research Communications (2000), 268(3), 784-789

CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

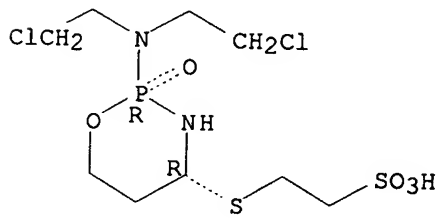
AB RhoB encoding a Ras-related GTPase is immediate-early inducible by genotoxic treatments. To address the question of the physiol. role of RhoB in cellular defense, cells stably overexpressing wild-type RhoB protein were generated. Overexpression of RhoB renders cells hypersensitive to the killing effect of alkylating agents including antineoplastic drugs but not to UV-light and doxorubicin. As compared to control cells, RhoB overexpressing cells revealed an increase in the frequency of alkylation-induced apoptotic cell death. This indicates that RhoB is involved in modulating apoptotic signaling. Furthermore, overexpression of RhoB resulted in a prolonged transient block to DNA replication upon MMS treatment. UV-induced replication blockage was not affected by RhoB. Based on the data we suggest RhoB to be a novel regulatory factor which takes influence on the level of cytotoxicity of DNA damaging drugs and forces cells to alkylation-induced apoptosis. The data indicate that this might be due to RhoB mediated delay in cell cycle progression upon alkylation treatment. (c) 2000 Academic Press.

IT **88859-04-5**, Mafosfamide
RL: ADV (Adverse effect, including toxicity); **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(RhoB in cellular response to genotoxic agent-induced DNA damage)

RN 88859-04-5 HCAPLUS

CN Ethanesulfonic acid, 2-[[(2R,4R)-2-[bis(2-chloroethyl)amino]tetrahydro-2-oxido-2H-1,3,2-oxazaphosphorin-4-yl]thio]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



CC 1-6 (Pharmacology)
Section cross-reference(s): 13

ST RhoB cytoprotection alkylating antitumor agent apoptosis; methyl methanesulfonate mafosfamide methylnitronitrosoguanidine genotoxicity RhoB drug resistance; cisplatin treosulfan hydrogen peroxide **radiation** DNA damage RhoB

IT Genotoxicity
Ionizing **radiation**
(RhoB in cellular response to genotoxic agent-induced DNA damage)

IT 66-27-3, Methyl methanesulfonate 70-25-7, N-Methyl-N'-nitro-N-nitrosoguanidine 299-75-2, Treosulfan 15663-27-1, Cisplatin **88859-04-5**, Mafosfamide
RL: ADV (Adverse effect, including toxicity); **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study);

USES (Uses)
(RhoB in cellular response to genotoxic agent-induced DNA damage)
REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 2 OF 5 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:14413 HCAPLUS
DOCUMENT NUMBER: 132:44646
TITLE: Total-body irradiation and melphalan is a safe and effective conditioning regimen for autologous bone marrow transplantation in children with acute myeloid leukemia in first remission
AUTHOR(S): Bonetti, F.; Zecca, M.; Pession, A.; Messina, C.; Montagna, D.; Lanino, E.; Fagioli, F.; Santoro, N.; Prete, A.; Cesaro, S.; Rondelli, R.; Giorgiani, G.; De Stefano, P.; Locatelli, F.
CORPORATE SOURCE: Italian Association for Pediatric Hematology and Oncology-Bone Marrow Transplantation Group, Department of Pediatrics, University of Pavia, IRCCS Policlinico San Matteo, Pavia, I-27100, Italy
SOURCE: Journal of Clinical Oncology (1999), 17(12), 3729-3735
CODEN: JCONDN; ISSN: 0732-183X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To evaluate the safety and efficacy of a preparative regimen consisting of fractionated total-body **radiation** (9.9 to 12 Gy) and melphalan (140 mg/m2 in a single dose) in children with acute myeloid leukemia in first complete remission (CR) given autologous bone marrow transplantation (ABMT). Fifty-three children (30 males and 23 females; age range, 1.5 to 18 yr) were enrolled onto the study. The median time from first CR to ABMT was 3.5 mo (range, 1.4 to 13 mo), with 45 patients (85%) undergoing transplantation within 6 mo from the diagnosis. Forty-five patients received in vitro marrow purging with std.-dose mafos-famide (100 .mu.g/mL), seven patients were treated with interleukin-2 before marrow collection, and in the remaining child, the marrow was unmanipulated. The median infused cell dose was 1.8 .times. 108/kg (range, 0.4 to 5.8 .times. 108/kg). All patients but one achieved hematopoietic engraftment, with a median time to neutrophil recovery of 24 days (range, 11 to 66 days). Treatment-related toxicity was moderate and consisted mainly of mucositis. One patient died from cytomegalovirus interstitial pneumonia, and one died from pulmonary hemorrhage. Fourteen patients (26%) relapsed at a median time of 6 mo after ABMT (range, 2 to 17 mo), with a cumulative relapse probability of 29% (95% confidence interval, 16% to 42%). The 5-yr Kaplan-Meier est. of survival for all 53 patients was 78% (range, 65% to 90%), whereas the overall 5-yr disease-free survival was 68% (range, 55% to 81%), with a median follow-up duration of 40 mo (range, 7 to 130 mo). These data suggest that, in our cohort of patients, the combination of total-body irradn. and melphalan is safe and assocd. with good antileukemia activity, making ABMT an appealing alternative for postremission therapy in children with acute myeloid leukemia in first CR.

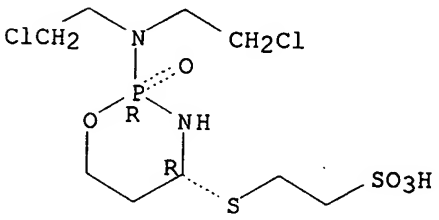
IT **88859-04-5**, Mafos-famide
RL: ADV (Adverse effect, including toxicity); **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study);
USES (Uses)
(effect of total-body irradn. and melphalan for autologous bone marrow

transplantation in children with acute myeloid leukemia in first remission)

RN 88859-04-5 HCAPLUS

CN Ethanesulfonic acid, 2-[[(2R,4R)-2-[bis(2-chloroethyl)amino]tetrahydro-2-oxido-2H-1,3,2-oxazaphosphorin-4-yl]thio]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



CC 1-6 (Pharmacology)
Section cross-reference(s): 8

IT 51-48-9, L-Thyroxin, biological studies 148-82-3, Melphalan **88859-04-5**, Mafos-famide
RL: ADV (Adverse effect, including toxicity); **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(effect of total-body irradn. and melphalan for autologous bone marrow transplantation in children with acute myeloid leukemia in first remission)

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1999:349876 HCAPLUS

DOCUMENT NUMBER: 131:141486

TITLE: The sulfhydryl containing compounds WR-2721 and glutathione as radio- and chemoprotective agents. A review, indications for use and prospects

AUTHOR(S): Hospers, G. A. P.; Eisenhauer, E. A.; De Vries, E. G. E.

CORPORATE SOURCE: Division of Medical Oncology, Department of Internal Medicine, University Hospital Groningen, Groningen, 9700 RB, Neth.

SOURCE: British Journal of Cancer (1999), 80(5/6), 629-638
CODEN: BJCAAI; ISSN: 0007-0920

PUBLISHER: Churchill Livingstone

DOCUMENT TYPE: Journal; General Review

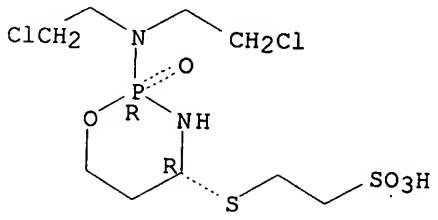
LANGUAGE: English

AB A review with over 80 refs. Radio- and chemotherapy for the treatment of malignancies are often assocd. with significant toxicity. One approach to reduce the toxicity is the concomitant treatment with chemoprotective agents. This article reviews two sulfhydryl compds., namely the agent WR-2721 (amifostine), a compd. recently registered for use in human in many countries, and the natural occurring compd. glutathione (GSH). GSH is not registered as a chemoprotective agent. WR-2721 is an aminothiol prodrug and has to be converted to the active compd. WR-1065 by membrane-bound alk. phosphatase. WR-1065 and GSH both act as naturally

occurring thiols. No protective effect on the tumor has been found when these compds. are administered i.v. There is even in vitro evidence for an increased anti-tumor effect with mafosfamide after pretreatment with WR-2721, and in vivo after treatment with carboplatin and paclitaxel. Randomized clin. studies have shown that WR-2721 and GSH decrease cisplatin-induced nephrotoxicity and that WR-2721 reduces **radiation** radiotherapy-induced toxicity. Side-effects assocd. with WR-2721 are nausea, vomiting and hypotension, GSH has no side-effects. An exact role of WR-2721 and GSH as chemoprotectors is not yet completely clear. Future studies should examine the protective effect of these drugs on mucositis, cardiac toxicity, neuro- and ototoxicity, the development of secondary neoplasms and their effect on quality of life.

IT **88859-04-5**, Mafosfamide
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(sulfhydryl contg. compds. as radio- and chemoprotective agents, and potentiating antitumor drug effects)
RN 88859-04-5 HCAPLUS
CN Ethanesulfonic acid, 2-[[(2R,4R)-2-[bis(2-chloroethyl)amino]tetrahydro-2-oxido-2H-1,3,2-oxazaphosphorin-4-yl]thio]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



CC 8-0 (Radiation Biochemistry)
IT Cytoprotective agents
Drug interactions
Radioprotectants
Radiotherapy
(sulfhydryl contg. compds. as radio- and chemoprotective agents, and potentiating antitumor drug effects)
IT 70-18-8, Glutathione, biological studies 20537-88-6, WR-2721 31098-42-7, WR-1065 33069-62-4, Paclitaxel 41575-94-4, Carboplatin **88859-04-5**, Mafosfamide
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(sulfhydryl contg. compds. as radio- and chemoprotective agents, and potentiating antitumor drug effects)
REFERENCE COUNT: 81 THERE ARE 81 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:153954 HCAPLUS
DOCUMENT NUMBER: 130:308474
TITLE: Activation of c-Jun N-terminal kinase 1 by UV irradiation is inhibited by wortmannin without affecting c-jun expression
AUTHOR(S): Fritz, G.; Kaina, B.
CORPORATE SOURCE: Institute of Toxicology, Division of Applied Toxicology, University of Mainz, Mainz, D-55131,

SOURCE: Germany
Molecular and Cellular Biology (1999), 19(3), 1768-1774
CODEN: MCEBD4; ISSN: 0270-7306
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

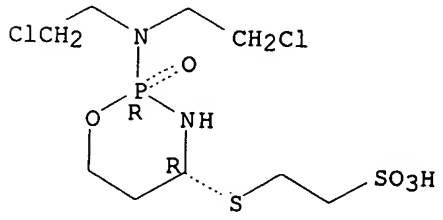
AB Activation of c-Jun N-terminal kinases (JNKs)/stress-activated protein kinases is an early response of cells upon exposure to DNA-damaging agents. JNK-mediated phosphorylation of c-Jun is currently understood to stimulate the transactivating potency of AP-1 (e.g., c-Jun/c-Fos; c-Jun/ATF-2), thereby increasing the expression of AP-1 target genes. Here we show that stimulation of JNK1 activity is not a general early response of cells exposed to genotoxic agents. Treatment of NIH 3T3 cells with UV light (UV-C) as well as with Me methanesulfonate (MMS) caused activation of JNK1 and an increase in c-Jun protein and AP-1 binding activity, whereas antineoplastic drugs such as mafosfamide, mitomycin C, N-hydroxyethyl-N-chloroethylnitrosourea, and treosulfan did not elicit this response. The phosphatidylinositol 3-kinase inhibitor wortmannin specifically blocked the UV-stimulated activation of JNK1 but did not affect UV-driven activation of extracellular regulated kinase 2 (ERK2). To investigate the significance of JNK1 for transactivation of c-jun, we analyzed the effect of UV irradn. on c-jun expression under conditions of wortmannin-mediated inhibition of UV-induced stimulation of JNK1. Neither the UV-induced increase in c-jun mRNA, c-Jun protein, and AP-1 binding nor the activation of the collagenase and c-jun promoters was affected by wortmannin. In contrast, the mitogen-activated protein kinase/ERK kinase inhibitor PD98059, which blocked ERK2 but not JNK1 activation by UV irradn., impaired UV-driven c-Jun protein induction and AP-1 binding. Based on the data, we suggest that JNK1 stimulation is not essential for transactivation of c-jun after UV exposure, whereas activation of ERK2 is required for UV-induced signaling leading to elevated c-jun expression.

IT **88859-04-5**, Mafosfamide
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(stimulation of JNK1 activity is not a general early response of cells exposed to genotoxic agents)

RN 88859-04-5 HCAPLUS

CN Ethanesulfonic acid, 2-[[(2R,4R)-2-[bis(2-chloroethyl)amino]tetrahydro-2-oxido-2H-1,3,2-oxazaphosphorin-4-yl]thio]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



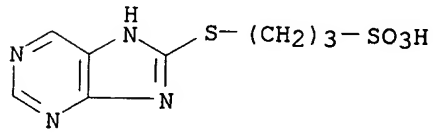
CC 8-6 (Radiation Biochemistry)
Section cross-reference(s): 1, 4

ST UV **radiation** wortmannin JNK1 ERK2 cjun

IT Mutagens

UV C **radiation**
(activation of c-Jun N-terminal kinase 1 by UV irradn. is inhibited by wortmannin without affecting c-jun expression)
IT 50-07-7, Mitomycin C 299-75-2, Treosulfan **88859-04-5**, Mafosfamide 128202-04-0
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(stimulation of JNK1 activity is not a general early response of cells exposed to genotoxic agents)
REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1986:621871 HCAPLUS
DOCUMENT NUMBER: 105:221871
TITLE: Relations between electronic and informational factors and the radioprotective effectiveness of sulfur-containing substances
AUTHOR(S): Mukhomorov, V. K.
CORPORATE SOURCE: S. M. Kirov Mil. Med. Acad., Leningrad, USSR
SOURCE: Radiobiologiya (1986), 26(4), 560-3
CODEN: RADOA8; ISSN: 0033-8192
DOCUMENT TYPE: Journal
LANGUAGE: Russian
AB The radioprotective activities of a no. of S-contg. compds. were analyzed in terms of the radioprotective information contained in their individual chem. constituents. A certain information threshold must be met before the substance is an effective radioprotectant.
IT **10200-87-0**
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(radioprotective effectiveness of, structural information in relation to)
RN 10200-87-0 HCAPLUS
CN 1-Propanesulfonic acid, 3-(1H-purin-8-ylthio)- (9CI) (CA INDEX NAME)



CC 8-10 (Radiation Biochemistry)
IT **Radioprotectants**
(sulfur-contg. compds., structure-function relation of, chem. information in relation to)
IT 638-43-7 694-59-7 758-28-1 1191-49-7 3687-18-1 3762-94-5
4378-70-5 4596-56-9 4621-66-3 5139-02-6 6197-31-5 7250-31-9
7704-34-9D, compds. **10200-87-0** 10319-70-7 13338-50-6
13368-86-0 13441-72-0 13514-29-9 13551-09-2 18771-14-7
20537-88-6 20709-39-1 20724-76-9 21668-81-5 25452-97-5
29146-57-4 31098-42-7 34725-75-2 44744-78-7 44957-28-0
50433-21-1 54978-25-5 56235-27-9 56643-49-3 70548-43-5
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105289-99-4 105290-00-4 105290-01-5 105290-02-6 105290-03-7
105290-04-8 105290-05-9 105290-06-0 105290-08-2 105290-09-3
105290-10-6 105290-11-7 105290-12-8 105313-87-9
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(radioprotective effectiveness of, structural information in relation to)

```
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L1                  STR

 S~G3          Ak~G1~Ak~G2          CH2Ak~G2          Ak~CH2G2          CH2G2
 1  2          @3  4  5  6          @7  8  9          @10 11 12         @13 14

 CH~O          CH~S                      28                29                30
@15 16        @17 18                     O                 O                 S
                                          ≀                 ≀                 ≀
                                    O~~S~~O           O~~P~~O           O~~P~~O
                                  19 @20 21         22 @23 24         25 @26 27

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VAR G2=20/23/26
VAR G3=3/7/10/13
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CONNECT IS E2  RC AT   3
CONNECT IS E2  RC AT   5
CONNECT IS E2  RC AT   8
CONNECT IS E2  RC AT  10
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CONNECT IS E1  RC AT  18
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  30

STEREO ATTRIBUTES: NONE
L2       1041700 SEA FILE=REGISTRY ABB=ON  PLU=ON  (S>1 AND O>2) OR (S>1 AND
                 P/ELS AND O>1) OR (S/ELS AND P/ELS AND O>2)
L3       1018440 SEA FILE=REGISTRY ABB=ON  PLU=ON  L2 NOT PMS/CI
L4        238689 SEA FILE=REGISTRY ABB=ON  PLU=ON  L3 AND NR<3
L13         1376 SEA FILE=REGISTRY SUB=L4 SSS FUL L1
L15         1264 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "RADIATION (L) EXPOSURE"/CT
L16         1098 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "RADIATION SICKNESS"/CT
L18            0 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L13 AND (L15 OR L16)
```

Zero exact matches

9 OF 39 USPATFULL
AN 90:9313 USPATFULL
TI Antioxidant thiohistidine compounds
IN Shapiro, Bennett M., Seattle, WA, United States
Turner, Eric E., Seattle, WA, United States
Hopkins, Paul B., Seattle, WA, United States
Klevit, Rachel E., Seattle, WA, United States
Holler, Tod P., Seattle, WA, United States
Spaltenstein, Andreas, Seattle, WA, United States
PA The Board of Regents of the University of Washington, Seattle, WA, United States (U.S. corporation)
PI US 4898878 19900206
AI US 1987-104736 19871002 (7)
DT Utility
FS Granted
EXNAM Primary Examiner: Schwartz, Richard A.
LREP Christensen, O'Connor, Johnson & Kindness
CLMN Number of Claims: 4
ECL Exemplary Claim: 1
DRWN 9 Drawing Figure(s); 8 Drawing Page(s)
LN.CNT 1618
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Therapeutic antioxidant compounds, useful for relieving the pathogenesis of oxidative stress, of formula ##STR1## wherein substituents R.sub.1, R.sub.2, R.sub.3, and R.sub.4 are individually selected from among hydrogen, methyl, or other atoms and groups that do not adversely affect the overall spectrum of redox activity of the 4-thiohistidine. N-3 is unsubstituted or is substituted as described for R.sub.1 to R.sub.4. R.sub.6 is preferably hydrogen or --SR.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD . . . intermediates (Misra, H. R., J. Biol. Chem. 249:2151-2155, 1974). Thiol toxicity may be due to redox cycling; for example, when **cystine** is given to cells it damages lipoproteins, apparently by being reduced to cysteine intracellularly then exiting to reoxidize and produce. . .
DETD . . . This readily studied, reproducible system allow us to assess whether cellular viability is enhanced by ovothiols at different levels of **radiation exposure** and how this correlates with the other properties of these aromatic thiols.

ANSWER 1 OF 27 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

AN 2002284730 EMBASE

TI Peripheral primitive neuroectodermal tumour during pregnancy.

AU Varveris H.; Mazonakis M.; Damilakis J.; Stefanaki K.; Lyraraki E.; Kachris S.; Orfanoudaki E.; Prassopoulos P.; Samonis G.

CS Dr. H. Varveris, Dept. of Radiotherapy and Oncology, Iraclion University Hospital, School of Medicine, 71110 Iraclion, Crete, Greece

SO British Journal of Radiology, (2002) 75/894 (543-547).
Refs: 16
ISSN: 0007-1285 CODEN: BJRAAP

CY United Kingdom

DT Journal; Article

FS 008 Neurology and Neurosurgery
014 Radiology
016 Cancer
050 Epilepsy
037 Drug Literature Index
010 Obstetrics and Gynecology

LA English

SL English

AB The case of a 25-year-old primipara in the second trimester of pregnancy, suffering from a peripheral primitive neuroectodermal tumour (pPNET) diagnosed by bone biopsy, is described. External irradiation was initially performed because of Jacksonian seizures due to a lesion in the right cerebral hemisphere. Appropriate shielding was used to reduce fetal exposure during brain radiotherapy. Caesarian delivery at the 27th week of gestation was performed because of tumour progression. The neonate had no evidence of disease and survived for 1 month. However, the placenta and ovaries showed metastases from the maternal pPNET. The patient died 14 months after initial diagnosis owing to the aggressiveness of the tumour, the rapid and extensive semination (bone marrow, lung, liver, craniospinal axis involvement) and the inability to adequately treat the patient with appropriate doses of chemotherapy.

CT Medical Descriptors:
*neuroectoderm tumor: DI, diagnosis
*neuroectoderm tumor: RT, radiotherapy
*second trimester pregnancy
human
case report
female
adult
bone biopsy
primigravida
seizure: CO, complication
seizure: RT, radiotherapy
right hemisphere
brain injury
brain radiation
radiation protection
prenatal exposure
radiation exposure
cesarean section
cancer growth
survival
placenta
metastasis: CO, complication
metastasis: DT, drug therapy
ovary metastasis: CO, complication
ovary metastasis: DT, drug therapy
death
bone marrow metastasis: CO, complication
bone marrow. . . drug therapy
spinal cord metastasis: PC, prevention
nuclear magnetic resonance imaging
thermoluminescence dosimeter
brain metastasis: CO, complication
radiation dose

article
ifosfamide: DT, drug therapy
ifosfamide: CB, drug combination
mesna: DT, drug therapy
mesna: CB, drug combination
mesna: IV, intravenous drug administration
etoposide: DT, drug therapy
etoposide: CB, drug combination
dactinomycin: DT, drug therapy
dactinomycin: CB, drug combination
doxorubicin: CB, drug combination
doxorubicin: DT,. . .

RN (ifosfamide) 3778-73-2; (**mesna**) 19767-45-4, 3375-50-6; (etoposide) 33419-42-0; (dactinomycin) 1402-38-6, 1402-58-0, 50-76-0; (doxorubicin) 23214-92-8, 25316-40-9; (vincristine) 57-22-7; (methotrexate) 15475-56-6, 59-05-2, 7413-34-5; (cytarabine) 147-94-4, 69-74-9;. . .

L3 ANSWER 2 OF 27 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2002111840 EMBASE
TI Protection of salivary function by intensity-modulated radiation therapy in patients with head and neck cancer.
AU Chao K.S.C.
CS Dr. K.S.C. Chao, Radiation Oncology Center, Washington Univ. School of Medicine, 4939 Children's Place, St Louis, MO 63110, United States
SO Seminars in Radiation Oncology, (2002) 12/1 SUPPL. 1 (20-25).
Refs: 25
ISSN: 1053-4296 CODEN: SRONEO
CY United States
DT Journal; Conference Article
FS 014 Radiology
016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB The degree of xerostomia has been reported to depend on the radiation dose and the salivary gland volume irradiated. Sparing salivary function can be achieved by reducing radiation dose to the salivary glands or using a radiation protector, such as amifostine (Ethyol). In this report, the author reviews clinical experiences in intensity-modulated radiation therapy (IMRT) for head and neck cancer. In experiences, the dosimetric advantage of IMRT did translate into significant reduction of late salivary toxicity in patients with oropharyngeal carcinoma. The author has found no adverse impact on tumor control and disease-free survival in patients treated with IMRT. Further, when studying the dose response of parotid gland after irradiation, it was found that the stimulated saliva flow 6 months after IMRT treatment reduced at approximately 4% per Gy exponentially of the mean parotid dose. The authors also review existing clinical data on the combination of amifostine and radiation and the potential therapeutic gain in combining IMRT with amifostine.
CT Medical Descriptors:
*salivation
*cancer . . . cancer: RT, radiotherapy
*neck cancer: RT, radiotherapy
xerostomia: CO, complication
xerostomia: DT, drug therapy
xerostomia: PC, prevention
salivary gland
radiation dose
dosimetry
oropharynx carcinoma: RT, radiotherapy
cancer control
cancer survival
dose response

radiation exposure
hypotension: SI, side effect
rash: SI, side effect
nausea: SI, side effect
drug effect
drug mechanism
human
clinical trial
conference paper
priority journal
amifostine: AE, adverse drug reaction
amifostine:. . . drug administration
amifostine: CM, drug comparison
amifostine: DT, drug therapy
amifostine: PD, pharmacology
amifostine: IV, intravenous drug administration
amifostine: SC, subcutaneous drug administration
razoxane: CM, drug comparison
mesna: CM, drug comparison
drug metabolite
wr 1605
unclassified drug
RN (amifostine) 20537-88-6; (razoxane) 21416-67-1, 21416-87-5, 24584-09-6, 24613-06-7; (**mesna**) 19767-45-4, 3375-50-6

L3 ANSWER 3 OF 27 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2001334106 EMBASE
TI Paediatric laryngeal carcinoma: Case report, literature review and possible role of agent orange.
AU Pham T.V.; Lannigan F.J.
CS Dr. T.V. Pham, 4 Johnson Street, Wembley, Perth, WA 6014, Australia
SO Australian Journal of Otolaryngology, (2001) 4/2 (136-139).
Refs: 27
ISSN: 1037-2105 CODEN: AJOTEQ
CY Australia
DT Journal; Article
FS 011 Otorhinolaryngology
007 Pediatrics and Pediatric Surgery
052 Toxicology
037 Drug Literature Index
014 Radiology
016 Cancer
LA English
SL English
AB Carcinoma of the larynx is a rare malignancy in the paediatric age group. A number of predisposing factors have been identified, including juvenile laryngeal papillomatosis (JLP), radiation and tobacco exposure, and cancer malformation syndromes. The case of a seven and a half year old boy with an undifferentiated carcinoma of the larynx is reported. There were no predisposing factors except for a history of exposure to Agent Orange by the biological father. The literature of juvenile laryngeal carcinoma will be reviewed including a possible link between laryngeal carcinoma and Agent Orange.
CT Medical Descriptors:
*larynx carcinoma: DT, drug therapy
*larynx carcinoma: SU, surgery
*larynx carcinoma: RT, radiotherapy
*pediatrics
human
case report
school child
male
larynx papillomatosis
risk factor
radiation
radiation exposure
drug exposure

malformation syndrome
father
cancer combination chemotherapy
salvage therapy
cancer radiotherapy
article
*herbicide: TO, drug toxicity
etoposide: DT, drug therapy
etoposide: CB, drug combination
mesna: DT, drug therapy
mesna: CB, drug combination
dimethoate: DT, drug therapy
dimethoate: CB, drug combination
carboplatin: DT, drug therapy
carboplatin: CB, drug combination

RN (etoposide) 33419-42-0; (**mesna**) 19767-45-4, 3375-50-6; (dimethoate) 60-51-5; (carboplatin) 41575-94-4

L3 ANSWER 4 OF 27 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

AN 1998141009 EMBASE

TI Metastatic angiosarcoma of the spleen after accidental **radiation exposure**: A case report.

AU Geffen D.B.; Zirkin H.J.; Mermershtain W.; Cohen Y.; Ariad S.

CS Dr. D.B. Geffen, Department of Oncology, Soroka Medical Center, Beer Sheva, Israel

SO American Journal of Clinical Oncology: Cancer Clinical Trials, (1998) 21/2 (167-170).
Refs: 20
ISSN: 0277-3732 CODEN: AJCODI

CY United States

DT Journal; Article

FS 016 Cancer
037 Drug Literature Index

LA English

SL English

AB Angiosarcoma is a rare malignant tumor arising from endothelial cells of blood vessels or lymphatic channels. Therapeutic irradiation, thoriumdioxide administration, pyothorax, and polyvinyl chloride exposure have been shown to be predisposing factors for developing angiosarcoma. Accidental **radiation exposure** has not been associated with angiosarcoma. We present an unusual case of angiosarcoma of the spleen, with metastases to bone, liver, breast, and bone marrow, in a woman who lived near the Chernobyl nuclear facility in the former Soviet Union at the time of the reactor accident in 1896. To the best of our knowledge, this is the first report of metastatic angiosarcoma after accidental **radiation exposure**.

TI Metastatic angiosarcoma of the spleen after accidental **radiation exposure**: A case report.

AB . . . Therapeutic irradiation, thoriumdioxide administration, pyothorax, and polyvinyl chloride exposure have been shown to be predisposing factors for developing angiosarcoma. Accidental **radiation exposure** has not been associated with angiosarcoma. We present an unusual case of angiosarcoma of the spleen, with metastases to bone,. . . reactor accident in 1896. To the best of our knowledge, this is the first report of metastatic angiosarcoma after accidental **radiation exposure**.

CT Medical Descriptors:
*angiosarcoma: DT, drug therapy
*angiosarcoma: ET, etiology
*spleen cancer: DT, drug therapy
*spleen cancer: ET, etiology
cancer risk
radiation exposure
chernobyl accident
bone metastasis: CO, complication
liver metastasis: CO, complication
breast metastasis: CO, complication

bone marrow metastasis: CO, complication
cancer combination chemotherapy
human
female
case report
article
doxorubicin: DT, drug therapy
ifosfamide: DT, drug therapy
mesna: DT, drug therapy
RN (doxorubicin) 23214-92-8, 25316-40-9; (ifosfamide) 3778-73-2; (**mesna**) 19767-45-4, 3375-50-6

L3 ANSWER 5 OF 27 USPATFULL
AN 2002:75189 USPATFULL
TI Method of treating complications in immunodepressed states resulting from HIV infection
IN Kozhemyakin, Andrei L., St. Petersburg, RUSSIAN FEDERATION
Sinackevich, Nickolai V., St. Petersburg, RUSSIAN FEDERATION
Seryi, Sergey V., St. Petersburg, RUSSIAN FEDERATION
Rakhilov, Alexei M., St. Petersburg, RUSSIAN FEDERATION
Morozov, Vyacheslav G., St. Petersburg, RUSSIAN FEDERATION
Khavinson, Vladimir Kh., St. Petersburg, RUSSIAN FEDERATION
PA Cytran, Inc., Kirkland, WA, United States (U.S. corporation)
PI US 6368788 B1 20020409
AI US 1997-977279 19971124 (8)
RLI Continuation of Ser. No. US 1995-452411, filed on 26 May 1995, now patented, Pat. No. US 5728680 Continuation-in-part of Ser. No. US 1994-278463, filed on 21 Jul 1994, now abandoned Continuation-in-part of Ser. No. US 1994-257495, filed on 7 Jun 1994, now abandoned Continuation of Ser. No. US 1991-783518, filed on 28 Oct 1991, now abandoned Continuation-in-part of Ser. No. US 1991-678129, filed on 1 Apr 1991, now abandoned
PRAI SU 1987-4352833 19871230
DT Utility
FS GRANTED
EXNAM Primary Examiner: Park, Hankyel
LREP Townsend and Townsend and Crew LLP
CLMN Number of Claims: 14
ECL Exemplary Claim: 1
DRWN 16 Drawing Figure(s); 8 Drawing Page(s)
LN.CNT 7640
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Methods of treatment of subjects for decreasing cell mediated autoimmunity or humoral autoimmunity by administering an R'-Glu-Trp-R" pharmaceutical preparation useful in subjects having autoimmune diseases.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD . . . usefuil inlcude e.g., Chlorambucil, Cyclophosphamide, Ifosfamide, Mechlorethamine Hydrochloride, Melphalan, Thiotepa, Busulfan, Procarbazine Hydrochloride, Carmustine, Lomustine, Streptozocin, Cisplatin, Carboplatin, Dacarbazine, Altretamine, **Mesna**, Methotrexate, Leucovorin Calcium, Cytarabine, Floxuridine, Fluorouracil, Cladribine, Fludarabine, Mercaptopurine, Pentostatin, Thioguanine, Hydroxyurea, Bleomycin Sulfate, Dactinomycin, Daunorubicin Hydrochloride, Doxorubicin Hydrochloride, Idarubicin. . . Hydroxyprogesterone Caproate, Medroxyprogesterone Acetate, Megestrol Acetate, Aminoglutethimide, Mitotane, Aldesleukin, Interferon-.alpha..sub.2a, BCG, Isotretinoin, Levamisole, Octreotide Acetate, Cyclophosphamide, Ifosfamide, Mechlorethamine Hydrochloride, Melphalan, **Mesna**, Busulfan, Carmustine, Lomustine, Nimustine, Semustine, Streptozocin, Cisplatin, Carboplatin, Iproplatin, Procarbazine Hydrochloride, Dacarbazine, Altretamine, Sodium Phosphate P.sup.32, Chromic Phosphate P.sup.32, Methotrexate,. . .
DETD . . . and patients with thoracic cavity tumors and other cancers after radiation therapy (EXAMPLE 3, Protocols A-C); ii) patients having occupational **radiation exposure** (EXAMPLE 12,

Protocols A and B); and, iii) patients following adult thymectomy (EXAMPLE 24). Illustrative examples of other immunocompromised patients. . .

DETD . . . World J Surgery 16(5): 918-923 (1992)). Hematological data have also been used to construct an empincal dose curve for gamma **radiation exposure** at Chernobyl and values reported for 127 of the former residents range from 0.5 Gy to 12 Gy (Konchalovskii, M.. . .

DETD Approximately 120,000 former Chernobyl residents are currently reportedly being followed to determine long term effects of **radiation exposure**. In patients suffering from acute radiation sickness during the accident, immune defects have been reported three to five years later. . .

DETD . . . and T- and B-lymphocyte populations were determined using a flow cytometer and monoclonal antibodies specific for lymphocyte cell surface markers. **Radiation exposure** levels for the different patients were determined using dosimetry data obtained by the military in Chemobyl using a D-2-P dosimeter.. . .

DETD . . . 2 that a response to the thymalin treatment was observed in the treatment population even at this early time after **radiation exposure** in Chernobyl.

DETD

TABLE 2

Thymalin Treatment of Chernobyl Subjects (X .+-. m):
Treatments Initiated Shortly after Accidental **Radiation Exposure**

Examination Group			
Healthy			
Laboratory Normal	Accidental **Radiation Exposure**		
Indicia.sup.a	Controls	Before	After Thymalin
Leukocytes, abs	5.7 .+-. 0.3	3.8 .+-. 0.3*	6.4 .+-. 0.8**
% Normal Value:	(100%)	(67%)	(112%)

Ratio. . .

DETD

TABLE 3

Treatment of Radiation-Induced Immunodeficiency: Treatments with Thymalin at Two Months Post-**Radiation Exposure** (X .+-. m)

Examination Group		
Healthy	Accidental Irradiation	
Normal	After Thymalin	
Indicia.sup.a	Control	Before Treatment
Leukocytes, abs	5.6 .+-. 0.8	3.5. . .

DETD . . . occur in subjects exposed to radiation, presumably because of decreased immune surveillance and elimination of tumor cells. At three years post-**radiation exposure**, preliminary evaluation of patients exposed to radiation at Chernobyl suggested lingering impaired immunity in 20% of the subjects as evidenced. . .

DETD

TABLE 6

Indices of Cellular Immunity and Innate Immunity in Chernobyl Subject Receiving Treatment with L-Glu-L-Trp at 3 Years Post-**Radiation Exposure**

Laboratory Test	Results	
Before	After	
Indicia	Therapy	Untreated L-Glu-L-Trp
Leukocytes, abs	5.8 .+-. 0.3	5.5 .+-. 1.0 5.6 .+-. 0.4
Lympho-	2.0 .+-.. . .	

DETD Occupational **Radiation Exposure**

DETD . . . in anti-bacterial, anti-viral, and anti-parasitic immunity. The

levels of lymphocytes in thymus, spleen, and lymph node are decreased following sub-lethal **radiation exposure**, and the effects of L-Glu-L-Trp on recovery of immune function following **radiation exposure** were investigated in this model.

L3 ANSWER 6 OF 27 USPATFULL
AN 2002:45604 USPATFULL
TI Method of treating snakebite and complications resulting therefrom
IN Lizcano, Lucinda, 743 W. Theo Ave., San Antonio, TX, United States 78225
PI US 6352979 B1 20020305
AI US 2001-933238 20010820 (9)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Henley, III, Raymond
LREP Dodd, Thomas J.
CLMN Number of Claims: 4
ECL Exemplary Claim: 1
DRWN 0 Drawing Figure(s); 0 Drawing Page(s)
LN.CNT 251
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to a method of treating snakebite victims, especially those at risk from neurotoxic effects from snakebite or those already exhibiting symptoms of neurotoxicity. The method includes administering to a patient in need of treatment an effective amount of a thiol or reducible disulfide compound according to the formula set forth in the specification.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM **Mesna** (sodium 2-mercaptoethene sulfonate) and **dimesna** (disodium 2,2'-dithiobis ethane sulfonate) are known therapeutic compounds that have heretofore demonstrated a wide variety of therapeutic uses. Both **mesna** and **dimesna** have been shown to be effective protective agents against certain specific types of toxicity associated with the administration of cytotoxic. . .
SUMM In particular, **mesna** has been used with some success in mitigating the toxic effects of cytotoxic agents such as ifosfamide, oxazaphosphorine, melphalane, cyclophosphamide,. . .
SUMM The near absence of toxicity of **dimesna** further underscores the usefulness of this compound, as large doses can be given to a patient without increasing the risk. . .
SUMM Further, pharmacological profiles of each compound indicate that, if proper conditions are maintained, **mesna** and **dimesna** do not prematurely inactivate primary therapeutic drugs to a significant degree. Thus, neither compound will significantly reduce activity of the. . .
SUMM The molecular structures of both **mesna** and **dimesna** are shown below as Structure I and Structure II respectively.
SUMM As shown, **dimesna** is a dimer of **mesna**, with the optimum conditions for oxidation occurring in the slightly basic (pH.about.7.3), oxygen rich environment found in blood plasma. In. . . in the presence of a reducing agent such as glutathione reductase, conditions prevalent in the kidneys, the primary constituent is **mesna**.
SUMM **Mesna** acts as a protective agent for a number of cytotoxic agents by substituting a nontoxic sulfhydryl moiety for a toxic hydroxy (or aquo) moiety. This action is particularly evidenced in the coadministration of **mesna** and oxazaphosphorine, and in the administration of **dimesna** along with certain platinum agents and/or taxanes.
SUMM **Dimesna**, as well as some analogues, have excellent toxicity profiles in mammalian species. In fact, **dimesna** has been administered intravenously to mice and dogs in doses higher than the accepted oral LD.sub.50 for common table salt (3750 mg/kg), with no adverse effects. **Dimesna** has also been administered to humans in doses exceeding 40 g/m.sup.2, with no adverse effects.
SUMM **Mesna**, and other analogues with free thiol moieties,

constitute the more physiologically active form of the two types of compounds described. . . terminal substitution at locations where a terminal leaving group of appropriate configuration, usually a hydroxy, aquo or superoxide is located. **Mesna** also tends to form conjugates with naturally occurring biochemicals that contain a free thiol moiety, such as cysteine, glutathione, homocysteine,. . .

SUMM **Dimesna** and other disulfides can be activated intracellularly by glutathione reductase, a ubiquitous enzyme, thereby generating high concentrations of intracellular free. . .

SUMM This profile is especially significant in explaining the success of **dimesna** in controlling and mitigating the toxic effects of platinum complex antitumor drugs. The mechanism for action in the case of. . .

SUMM **Mesna**, **dimesna**, and analogues of these compounds have been the subject of several prior pharmaceutical uses described in the literature and in. . . vitro, against a multiplicity of biological targets, and have been effective, in vivo, in the treatment of sickle cell disease, **radiation exposure**, chemical agent exposure, and other uses.

SUMM **Mesna**, **dimesna**, and analogues thereof are synthesized from commonly available starting materials, using acceptable routes well known in the art. One such method involves the two-step, single pot synthetic process for making **dimesna** and like compounds of the following formula:

SUMM . . . conversion of an alkenyl sulfonate salt or acid to the desired formula I compound. The process in the case of **mesna** is a single step process that converts the alkenyl sulfonate salt to **mesna** or a **mesna** derivative by reacting with an alkali metal sulfide or with hydrogen sulfide.

SUMM If the desired end product is **dimesna** or a **dimesna** analogue, a two-step single pot process is involved. Step 1 is as described above. Step 2 of the process is performed in the same reaction vessel as Step 1 without the need to purify or isolate the **mesna** formed during that step. Step 2 includes the introduction of oxygen gas into the vessel, along with an increase in pressure and temperature above ambient values, at least 20 pounds per square inch (psi) and at least 60.degree. C. **Dimesna** or a derivative thereof is formed in essentially quantitative yield.

SUMM Other processes, well known and documented in the prior art, may be employed to make either **mesna** or **dimesna**, or derivatives and analogues thereof.

L3 ANSWER 7 OF 27 USPATFULL
AN 2001:158265 USPATFULL
TI Method of treating inflammatory bowel disorders
IN Hausheer, Frederick H., 203 Kendall Pkwy., Boerne, TX, United States 78229
Peddaiahgari, Seetharamulu, 1207 Fawn Haven, San Antonio, TX, United States 78248
PI US 6291441 B1 20010918
AI US 2000-671791 20000927 (9)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Krass, Frederick
LREP Dodd, Thomas J.
CLMN Number of Claims: 4
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 241
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to a method of treating patients suffering from the inflammatory bowel disorders. The method includes administering to a patient in need of treatment an effective amount of a thiol or reducible disulfide compound according to the formula set forth in the specification.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM **Mesna** (sodium 2-mercaptoethene sulfonate) and **dimesna** (disodium 2,2'-dithiobis ethane sulfonate) are known therapeutic compounds that have heretofore demonstrated a wide variety of therapeutic uses. Both **mesna** and **dimesna** have been shown to be effective protective agents against certain specific types of toxicity associated with the administration of cytotoxic. . .

SUMM In particular, **mesna** has been used with some success in mitigating the toxic effects of cytotoxic agents such as ifosfamide, oxazaphosphorine, melphalane, cyclophosphamide,. . .

SUMM The near absence of toxicity of **dimesna** further underscores the usefulness of this compound, as large doses can be given to a patient without increasing the risk. . .

SUMM Further, pharmacological profiles of each compound indicate that, if proper conditions are maintained, **mesna** and diimesna do not prematurely inactivate primary therapeutic drugs to a significant degree. Thus, neither compound will significantly reduce activity. . .

SUMM The molecular structures of both **mesna** and **dimesna** are shown below as Structure I and Structure II respectively.

SUMM As shown, **dimesna** is a dimer of **mesna**, with the optimum conditions for oxidation occurring in the slightly basic (pH .about.7.3), oxygen rich environment found in blood plasma.. . . in the presence of a reducing agent such as glutathione reductase, conditions prevalent in the kidneys, the primary constituent is **mesna**.

SUMM **Mesna** acts as a protective agent for a number of cytotoxic agents by substituting a nontoxic sulfhydryl moiety for a toxic hydroxy (or aguo) moiety. This action is particularly evidenced in the coadministration of **mesna** and oxazaphosphorine, and in the administration of **dimesna** along with certain platinum agents and/or taxanes.

SUMM **Dimesna**, as well as some analogues, have excellent toxicity profiles in mammalian species. In fact, **dimesna** has been administered intravenously to mice and dogs in doses higher than the accepted oral LD.sub.50 for common table salt (3750 mg/kg), with no adverse effects. **Dimesna** has also been administered to humans in doses exceeding 40 g/m.sup.2, with no adverse effects.

SUMM **Mesna**, and other analogues with free thiol moieties, constitute the more physiologically active form of the two types of compounds described. . . terminal substitution at locations where a terminal leaving group of appropriate configuration, usually a hydroxy, aquo or superoxide is located. **Mesna** also tends to form conjugates with naturally occurring biochemicals that contain a free thiol moiety, such as cysteine, glutathione, homocysteine,. . .

SUMM **Dimesna** and other disulfides can be activated intracellulary by glutathione reductase, a ubiquitous enzyme, thereby generating high concentrations of intracellular free. . .

SUMM This profile is especially significant in explaining the success of **dimesna** in controlling and mitigating the toxic effects of platinum complex antitumor drugs. The mechanism for action in the case of. . .

SUMM **Mesna**, **dimesna**, and analogues of these compounds have been the subject of several prior pharmaceutical uses described in the literature and in. . . vitro, against a multiplicity of biological targets, and have been effective, in vivo, in the treatment of sickle cell disease, **radiation exposure**, chemical agent exposure, and other uses.

SUMM **Mesna**, **dimesna**, and analogues thereof are synthesized from commonly available starting materials, using acceptable routes well known in the art. One such method involves the two-step, single pot synthetic process for making **dimesna** and like compounds of the following formula:

SUMM . . . conversion of an alkenyl sulfonae salt or acid to the desired formula I compound. The process in the case of **mesna** is a single step process that converts the alkenyl sulfonate salt to **mesna** or a **mesna** derivative by reacting with an alkali metal sulfide or with hydrogen sulfide.

SUMM If the desired end product is **dimesna** or a **dimesna**

analogue, a two-step single pot process is involved. Step 1 is as described above. Step 2 of the process is performed in the same reaction vessel as Step 1 without the need to purify or isolate the **mesna** formed during that step. Step 2 includes the introduction of oxygen gas into the vessel, along with an increase in pressure and temperature above ambient values, at least 20 pounds per square inch (psi) and at least 60.degree. C. **Dimesna** or a derivative thereof is formed in essentially quantitative yield.

SUMM Other processes, well known and documented in the prior art, may be employed to make either **mesna** or **dimesna**, or derivatives and analogues thereof.

L3 ANSWER 8 OF 27 USPATFULL
AN 2001:131337 USPATFULL
TI Method of treating diabetic ophthalmopathy
IN Hausheer, Frederick H., 203 Kendall Pkwy., Boerne, TX, United States 78015
Parker, Aulma, 16650 Huebner Rd., No. 935, San Antonio, TX, United States 78248
Peddaiaghari, Seetharamulu, 1207 Fawn Haven, San Antonio, TX, United States 78248
PI US 6274622 B1 20010814
AI US 1999-427812 19991027 (9)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Fay, Zohreh
LREP Dodd, Thomas J.
CLMN Number of Claims: 4
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 264
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to a method of treating patients afflicted with diabetic ophthalmopathy. The method includes administering to a patient in need of treatment an effective amount of a thiol or reducible disulfide compound according to the formula set forth in the specification.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM **Mesna** (sodium 2-mercaptoethene sulfonate) and **dimesna** (disodium 2,2'-dithiobis ethane sulfonate) are known therapeutic compounds, which have heretofore demonstrated a wide variety of therapeutic uses. Both **mesna** and **dimesna** have been shown to be effective protective agents against certain specific types of toxicity associated with the administration of cytotoxic drugs used to treat patients for various types of cancer. In particular, **mesna** has been used with some success in mitigating the toxic effects of cytotoxic agents such as ifosfamide, oxazaphosphorine, melphalane, cyclophosphamide,. . .
SUMM The near absence of toxicity of **dimesna** further underscores the usefulness of this compound, as large doses that can be given to a patient without increasing the. . .
SUMM Further, pharmacological profiles of each compound indicate that, if proper conditions are maintained, **mesna** and **dimesna** do not prematurely inactivate primary therapeutic drugs to a significant degree. Thus, neither compound will significantly reduce activity of the. . .
SUMM The structures of both **mesna** and **dimesna** are shown below as Formula a and Formula b respectively.
SUMM As is well known, **dimesna** is a dimer of **mesna**, with the optimum conditions for oxidation occurring in the slightly basic (pH .about.7.3), oxygen rich environment found in blood plasma.. . . reducing agent such as glutathione reductase, conditions prevalent in the kidneys, intracellular spaces, intestines, and others, the primary constituent is **mesna**.
SUMM **Mesna** acts as a protective agent for a number of cytotoxic agents by substituting a nontoxic sulfhydryl moiety for a toxic hydroxy

(or aquo) moiety. This action is particularly evidenced in the coadministration of **mesna** and oxazaphosphorine, and in the administration of **dimesna** along with cisplatin, carboplatin, and taxane derivatives, as well as with other cytotoxic or cytostatic agents.

SUMM **Mesna** and **dimesna**, as well as some analogues of these compounds, have excellent toxicity profiles in mammalian species. In fact, **dimesna** has been administered intravenously to mice and dogs in doses higher than the accepted oral LD.sub.50 for common table salt (3750 mg/kg), with no adverse effects. **Dimesna** has also been administered to humans in doses exceeding 15 g/m.sup.2, with no adverse effects.

SUMM **Mesna**, and other analogues with free thiol moieties, constitute the more physiologically active form of the two types of compounds described. . .

SUMM **Dimesna** and other disulfides can be activated intracellularly by glutathione reductase, a ubiquitous enzyme, thereby generating high concentrations of intracellular free. . .

SUMM This profile is especially significant in explaining the success of **dimesna** in controlling and mitigating the toxic effects of platinum complex antitumor drugs. The mechanism for action in the case of. . .

SUMM **Mesna**, **dimesna**, and analogues of these compounds have been the subject of several prior pharmaceutical uses described in the literature and in. . . vitro, against a multiplicity of biological targets, and have been effective, in vivo, in the treatment of sickle cell disease, **radiation exposure**, chemical agent exposure, and other uses.

SUMM **Mesna**, **dimesna**, and analogues thereof are synthesized from commonly available starting materials, using acceptable routes well known in the art. One such method involves the two-step, single pot synthetic process for making **dimesna** and like compounds of the following formula:

SUMM . . . conversion of an alkenyl sulfonate salt or acid to the desired formula I compound. The process in the case of **mesna** is a single step process, which converts the alkenyl sulfonate salt to **mesna** or a **mesna** derivative by reacting with an alkali metal sulfide or with hydrogen sulfide.

SUMM If the desired end product is **dimesna** or a **dimesna** analogue, a two-step single pot process is involved. Step 1 is as described above. Step 2 of the process is performed in the same reaction vessel as Step 1 without the need to purify or isolate the **mesna** formed during that step. Step 2 includes the introduction of oxygen gas into the vessel, along with an increase in pressure and temperature above ambient values, at least 20 pounds per square inch (psi) and at least 60.degree. C. **Dimesna** or a derivative thereof is formed in essentially quantitative yield.

SUMM Other processes, well known and documented in the prior art, may be employed to make either **mesna** or **dimesna**, or derivatives and analogues thereof.

DETD Briefly, **Dimesna** (0-20 .mu.M) was incubated at 37.degree. C. with aldose reductase (0.0016 units, human recombinant, expressed in SF 9 cells) and. . .

DETD Aldose reductase assays were as described above. **Dimesna** (0-30 mM) was evaluated for its effect on the NADPH dependent reduction of glyceraldehyde (0.050-6 mM) to aldose at 37.degree.. . .

L3 ANSWER 9 OF 27 USPATFULL
AN 2001:102865 USPATFULL
TI Method of inhibiting angiogenesis
IN Peddaiahgari, Seetharamulu, 1207 Fawn Haven, San Antonio, TX, United States 78248
PI US 6255355 B1 20010703
AI US 2001-756033 20010106 (9)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Henley, III, Raymond

LREP Dodd, Thomas J.
CLMN Number of Claims: 4
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 217
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to a method of treating patients in need of angiogenesis inhibition. The method includes administering to a patient in need of treatment an effective amount of a thiol or reducible disulfide compound according to the formula set forth in the specification.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM **Mesna** (sodium 2-mercaptoethene sulfonate) and **dimesna** (disodium 2,2'-dithiobis ethane sulfonate) are known therapeutic compounds that have heretofore demonstrated a wide variety of therapeutic uses. Both **mesna** and **dimesna** have been shown to be effective protective agents against certain specific types of toxicity associated with the administration of cytotoxic. . .
SUMM In particular, **mesna** has been used with some success in mitigating the toxic effects of cytotoxic agents such as ifosfamide, oxazaphosphorine, melphalane, cyclophosphamide,. . .
SUMM The near absence of toxicity of **dimesna** further underscores the usefulness of this compound, as large doses can be given to a patient without increasing the risk. . .
SUMM Further, pharmacological profiles of each compound indicate that, if proper conditions are maintained, **mesna** and **dimesna** do not prematurely inactivate primary therapeutic drugs to a significant degree. Thus, neither compound will significantly reduce activity of the. . .
SUMM The molecular structures of both **mesna** and **dimesna** are shown below as Structure I and Structure II respectively.
SUMM As shown, **dimesna** is a dimer of **mesna**, with the optimum conditions for oxidation occurring in the slightly basic (pH.about.7.3), oxygen rich environment found in blood plasma. In. . . in the presence of a reducing agent such as glutathione reductase, conditions prevalent in the kidneys, the primary constituent is **mesna**.
SUMM **Mesna** acts as a protective agent for a number of cytotoxic agents by substituting a nontoxic sulfhydryl moiety for a toxic hydroxy (or aquo) moiety. This action is particularly evidenced in the coadministration of **mesna** and oxazaphosphorine, and in the administration of **dimesna** along with certain platinum agents and/or taxanes.
SUMM **Dimesna**, as well as some analogues, have excellent toxicity profiles in mammalian species. In fact, **dimesna** has been administered intravenously to mice and dogs in doses higher than the accepted oral LD.sub.50 for common table salt (3750 mg/kg), with no adverse effects. **Dimesna** has also been administered to humans in doses exceeding 40 g/m.sup.2, with no adverse effects.
SUMM **Mesna**, and other analogues with free thiol moieties, constitute the more physiologically active form of the two types of compounds described. . . terminal substitution at locations where a terminal leaving group of appropriate configuration, usually a hydroxy, aquo or superoxide is located. **Mesna** also tends to form conjugates with naturally occurring biochemicals that contain a free thiol moiety, such as cysteine, glutathione, homocysteine,. . .
SUMM **Dimesna** and other disulfides can be activated intracellularly by glutathione reductase, a ubiquitous enzyme, thereby generating high concentrations of intracellular free. . .
SUMM This profile is especially significant in explaining the success of **dimesna** in controlling and mitigating the toxic effects of platinum complex antitumor drugs. The mechanism for action in the case of. . .
SUMM **Mesna**, **dimesna**, and analogues of these compounds have been the subject of several prior pharmaceutical uses described in the literature and in. . . vitro, against a multiplicity of

biological targets, and have been effective, in vivo, in the treatment of sickle cell disease, **radiation exposure**, chemical agent exposure, and other uses.

SUMM **Mesna**, **dimesna**, and analogues thereof are synthesized from commonly available starting materials, using acceptable routes well known in the art. One such method involves the two-step, single pot synthetic process for making **dimesna** and like compounds of the following formula:

SUMM . . . conversion of an alkenyl sulfonate salt or acid to the desired formula I compound. The process in the case of **mesna** is a single step process that converts the alkenyl sulfonate salt to **mesna** or a **mesna** derivative by reacting with an alkali metal sulfide or with hydrogen sulfide.

SUMM If the desired end product is **dimesna** or a **dimesna** analogue, a two-step single pot process is involved. Step 1 is as described above. Step 2 of the process is performed in the same reaction vessel as Step 1 without the need to purify or isolate the **mesna** formed during that step. Step 2 includes the introduction of oxygen gas into the vessel, along with an increase in pressure and temperature above ambient values, at least 20 pounds per square inch (psi) and at least 60.degree. C. **Dimesna** or a derivative thereof is formed in essentially quantitative yield.

SUMM Other processes, well known and documented in the prior art, may be employed to make either **mesna** or **dimesna**, or derivatives and analogues thereof.

L3 ANSWER 10 OF 27 USPATFULL

AN 2001:97903 USPATFULL

TI Method of treating diabetic angiopathy

IN Hausheer, Frederick H., 203 Kendall Pkwy., Boerne, TX, United States 78015
Parker, Aulma, 16650 Huebner Rd., No. 935, San Antonio, TX, United States 78248
Peddaiaghari, Seetharamulu, 1207 Fawn Haven, San Antonio, TX, United States 78248

PI US 6251881 B1 20010626

AI US 1999-422478 19991021 (9)

DT Utility

FS GRANTED

EXNAM Primary Examiner: Cook, Rebecca

LREP Dodd, Thomas J

CLMN Number of Claims: 4

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 263

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention relates to a method of treating patients afflicted with diabetic angiopathy. The method includes administering to a patient in need of treatment an effective amount of a thiol or reducible disulfide compound according to the formula set forth in the specification.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM **Mesna** (sodium 2-mercaptoethene sulfonate) and **dimesna** (disodium 2,2'-dithiobis ethane sulfonate) are known therapeutic compounds, which have heretofore demonstrated a wide variety of therapeutic uses. Both **mesna** and **dimesna** have been shown to be effective protective agents against certain specific types of toxicity associated with the administration of cytotoxic drugs used to treat patients for various types of cancer. In particular, **mesna** has been used with some success in mitigating the toxic effects of cytotoxic agents such as ifosfamide, oxazaphosphorine, melphalane, cyclophosphamide,. . .

SUMM The near absence of toxicity of **dimesna** further underscores the usefulness of this compound, as large doses that can be given to a patient without increasing the. . .

SUMM Further, pharmacological profiles of each compound indicate that, if proper conditions are maintained, **mesna** and **dimesna**

do not prematurely inactivate primary therapeutic drugs to a significant degree. Thus, neither compound will significantly reduce activity of the. . .

SUMM The structures of both **mesna** and **dimesna** are shown below as Formula a and Formula b respectively.

SUMM As is well known, **dimesna** is a dimer of **mesna**, with the optimum conditions for oxidation occurring in the slightly basic (pH .about.7.3), oxygen rich environment found in blood plasma.. . . reducing agent such as glutathione reductase, conditions prevalent in the kidneys, intracellular spaces, intestines, and others, the primary constituent is **mesna**.

SUMM **Mesna** acts as a protective agent for a number of cytotoxic agents by substituting a nontoxic sulfhydryl moiety for a toxic hydroxy (or aquo) moiety. This action is particularly evidenced in the coadministration of **mesna** and oxazaphosphorine, and in the administration of **dimesna** along with cisplatin, carboplatin, and taxane derivatives.

SUMM **Mesna** and **dimesna**, as well as some analogues of these compounds, have excellent toxicity profiles in mammalian species. In fact, **dimesna** has been administered intravenously to mice and dogs in doses higher than the accepted oral LD.sub.50 for common table salt (3750 mg/kg), with no adverse effects. **Dimesna** has also been administered to humans in doses exceeding 15 g/m.sup.2, with no adverse effects.

SUMM **Mesna**, and other analogues with free thiol moieties, constitute the more physiologically active form of the two types of compounds described. . .

SUMM **Dimesna** and other disulfides can be activated intracellularly by glutathione reductase, a ubiquitous enzyme, thereby generating high concentrations of intracellular free. . .

SUMM This profile is especially significant in explaining the success of **dimesna** in controlling and mitigating the toxic effects of platinum complex antitumor drugs. The mechanism for action in the case of. . .

SUMM **Mesna**, **dimesna**, and analogues of these compounds have been the subject of several prior pharmaceutical uses described in the literature and in. . . vitro, against a multiplicity of biological targets, and have been effective, in vivo, in the treatment of sickle cell disease, **radiation exposure**, chemical agent exposure, and other uses.

SUMM **Mesna**, **dimesna**, and analogues thereof are synthesized from commonly available starting materials, using acceptable routes well known in the art. One such method involves the two-step, single pot synthetic process for making **dimesna** and like compounds of the following formula:

SUMM . . . conversion of an alkenyl sulfonate salt or acid to the desired formula I compound. The process in the case of **mesna** is a single step process, which converts the alkenyl sulfonate salt to **mesna** or a **mesna** derivative by reacting with an alkali metal sulfide or with hydrogen sulfide.

SUMM If the desired end product is **dimesna** or a **dimesna** analogue, a two-step single pot process is involved. Step 1 is as described above. Step 2 of the process is performed in the same reaction vessel as Step 1 without the need to purify or isolate the **mesna** formed during that step. Step 2 includes the introduction of oxygen gas into the vessel, along with an increase in pressure and temperature above ambient values, at least 20 pounds per square inch (psi) and at least 60.degree. C. **Dimesna** or a derivative thereof is formed in essentially quantitative yield.

SUMM Other processes, well known and documented in the prior art, may be employed to make either **mesna** or **dimesna**, or derivatives and analogues thereof.

DETD Briefly, **Dimesna** (0-20 .mu.M) was incubated at 37.degree. C. with aldose reductase (0.0016 units, human recombinant, expressed in SF 9 cells) and. . .

DETD Aldose reductase assays were as described above. **Dimesna** (0-30 mM) was evaluated for its effect on the NADPH dependent reduction of

glyceraldehyde (0.050-6 mM) to aldose at 37.degree.. . .

L3 ANSWER 11 OF 27 USPATFULL
AN 2001:86516 USPATFULL
TI Method of treating alcoholism and complications resulting therefrom
IN Peddaiahgari, Seetharamulu, San Antonio, TX, United States
PA BioNumerik Pharmaceuticals, Inc., San Antonio, TX, United States (U.S. corporation)
PI US 6245815 B1 20010612
AI US 2000-551982 20000415 (9)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Henley, III, Raymond
LREP Dodd, Thomas J.
CLMN Number of Claims: 4
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 243
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to a method of treating patients afflicted with alcoholism. The method includes administering to a patient in need of treatment an effective amount of a thiol or reducible disulfide compound according to the formula set forth in the specification.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM **Mesna** (sodium 2-mercaptoethene sulfonate) and **dimesna** (disodium 2,2'-dithiobis ethane sulfonate) are known therapeutic compounds that have heretofore demonstrated a wide variety of therapeutic uses. Both **mesna** and **dimesna** have been shown to be effective protective agents against certain specific types of toxicity associated with the administration of cytotoxic. . .
SUMM In particular, **mesna** has been used with some success in mitigating the toxic effects of cytotoxic agents such as ifosfamide, oxazaphosphorine, melphalane, cyclophosphamide,. . .
SUMM The near absence of toxicity of **dimesna** further underscores the usefulness of this compound, as large doses can be given to a patient without increasing the risk. . .
SUMM Further, pharmacological profiles of each compound indicate that, if proper conditions are maintained, **mesna** and **dimesna** do not prematurely inactivate primary therapeutic drugs to a significant degree. Thus, neither compound will significantly reduce activity of the. . .
SUMM The molecular structures of both **mesna** and **dimesna** are shown below as Structure I and Structure II respectively.
SUMM As shown, **dimesna** is a dimer of **mesna**, with the optimum conditions for oxidation occurring in the slightly basic (pH.about.7.3), oxygen rich environment found in blood plasma. In. . . in the presence of a reducing agent such as glutathione reductase, conditions prevalent in the kidneys, the primary constituent is **mesna**.
SUMM **Mesna** acts as a protective agent for a number of cytotoxic agents by substituting a nontoxic sulfhydryl moiety for a toxic hydroxy (or aquo) moiety. This action is particularly evidenced in the coadministration of **mesna** and oxazaphosphorine, and in the administration of **dimesna** along with certain platinum agents and/or taxanes.
SUMM **Dimesna**, as well as some analogues, have excellent toxicity profiles in mammalian species. In fact, **dimesna** has been administered intravenously to mice and dogs in doses higher than the accepted oral LD.sub.50 for common table salt (3750 mg/kg), with no adverse effects. **Dimesna** has also been administered to humans in doses exceeding 40 g/m.sup.2, with no adverse effects.
SUMM **Mesna**, and other analogues with free thiol moieties, constitute the more physiologically active form of the two types of compounds described. . . terminal substitution at locations where a terminal leaving group of appropriate configuration, usually a hydroxy, aquo or superoxide is located. **Mesna** also tends to form

conjugates with naturally occurring biochemicals that contain a free thiol moiety, such as cysteine, glutathione, homocysteine,. . .

SUMM **Dimesna** and other disulfides can be activated intracellularly by glutathione reductase, a ubiquitous enzyme, thereby generating high concentrations of intracellular free. . .

SUMM This profile is especially significant in explaining the success of **dimesna** in controlling and mitigating the toxic effects of platinum complex antitumor drugs. The mechanism for action in the case of. . .

SUMM **Mesna**, **dimesna**, and analogues of these compounds have been the subject of several prior pharmaceutical uses described in the literature and in. . . vitro, against a multiplicity of biological targets, and have been effective, in vivo, in the treatment of sickle cell disease, **radiation exposure**, chemical agent exposure, and other uses.

SUMM **Mesna**, **dimesna**, and analogues thereof are synthesized from commonly available starting materials, using acceptable routes well known in the art. One such method involves the two-step, single pot synthetic process for making **dimesna** and like compounds of the following formula:

SUMM . . . conversion of an alkenyl sulfonate salt or acid to the desired formula I compound. The process in the case of **mesna** is a single step process that converts the alkenyl sulfonate salt to **mesna** or a **mesna** derivative by reacting with an alkali metal sulfide or with hydrogen sulfide.

SUMM If the desired end product is **dimesna** or a **dimesna** analogue, a two-step single pot process is involved. Step 1 is as described above. Step 2 of the process is performed in the same reaction vessel as Step 1 without the need to purify or isolate the **mesna** formed during that step. Step 2 includes the introduction of oxygen gas into the vessel, along with an increase in pressure and temperature above ambient values, at least 20 pounds per square inch (psi) and at least 60.degree. C. **Dimesna** or a derivative thereof is formed in essentially quantitative yield.

SUMM Other processes, well known and documented in the prior art, may be employed to make either **mesna** or **dimesna**, or derivatives and analogues thereof.

L3 ANSWER 12 OF 27 USPATFULL
AN 2001:63672 USPATFULL
TI Method of treating acetaminophen overdose
IN Hausheer, Frederick H., 203 Kendall Pkwy., Boerne, TX, United States 78229
Peddaiahgari, Seetharamulu, 1207 Fawn Haven, San Antonio, TX, United States 78248
PI US 6225295 B1 20010501
AI US 2000-671792 20000927 (9)
DT Utility
FS Granted
EXNAM Primary Examiner: Spivack, Phyllis G.
LREP Dodd, Thomas J.
CLMN Number of Claims: 4
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 232
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method of treating patients suffering from acetaminophen overdose is disclosed. The method comprises administering to a patient in need of treatment an effective amount of a thiol or reducible disulfide compound according to the formula set forth in the specification.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM **Mesna** (sodium 2-mercaptoethene sulfonate) and **dimesna** (disodium 2,2'-dithiobis ethane sulfonate) are known therapeutic compounds that have heretofore demonstrated a wide variety of therapeutic uses. Both **mesna** and **dimesna** have been shown to be effective protective agents against certain specific types

of toxicity associated with the administration of cytotoxic. . .

SUMM In particular, **mesna** has been used with some success in mitigating the toxic effects of cytotoxic agents such as ifosfamide, oxazaphosphorine, melphalane, cyclophosphamide,. . .

SUMM The near absence of toxicity of **dimesna** further underscores the usefulness of this compound, as large doses can be given to a patient without increasing the risk. . .

SUMM Further, pharmacological profiles of each compound indicate that, if proper conditions are maintained, **mesna** and **dimesna** do not prematurely inactivate primary therapeutic drugs to a significant degree. Thus, neither compound will significantly reduce activity of the. . .

SUMM The molecular structures of both **mesna** and **dimesna** are shown below as Structure I and Structure II respectively.

SUMM As shown, **dimesna** is a dimer of **mesna**, with the optimum conditions for oxidation occurring in the slightly basic (pH .about.7.3), oxygen rich environment found in blood plasma.. . . in the presence of a reducing agent such as glutathione reductase, conditions prevalent in the kidneys, the primary constituent is **mesna**.

SUMM **Mesna** acts as a protective agent for a number of cytotoxic agents by substituting a nontoxic sulfhydryl moiety for a toxic hydroxy (or aquo) moiety. This action is particularly evidenced in the coadministration of **mesna** and oxazaphosphorine, and in the administration of **dimesna** along with certain platinum agents and/or taxanes.

SUMM **Dimesna**, as well as some analogues, have excellent toxicity profiles in mammalian species. In fact, **dimesna** has been administered intravenously to mice and dogs in doses higher than the accepted oral LD.sub.50 for common table salt (3750 mg/kg), with no adverse effects. **Dimesna** has also been administered to humans in doses exceeding 40 g/m.sup.2, with no adverse effects.

SUMM **Mesna**, and other analogues with free thiol moieties, constitute the more physiologically active form of the two types of compounds described. . . terminal substitution at locations where a terminal leaving group of appropriate configuration, usually a hydroxy, aquo or superoxide is located. **Mesna** also tends to form conjugates with naturally occurring biochemicals that contain a free thiol moiety, such as cysteine, glutathione, homocysteine,. . .

SUMM **Dimesna** and other disulfides can be activated intracellularly by glutathione reductase, a ubiquitous enzyme, thereby generating high concentrations of intracellular free. . .

SUMM This profile is especially significant in explaining the success of **dimesna** in controlling and mitigating the toxic effects of platinum complex antitumor drugs. The mechanism for action in the case of. . .

SUMM **Mesna**, **dimesna**, and analogues of these compounds have been the subject of several prior pharmaceutical uses described in the literature and in. . . vitro, against a multiplicity of biological targets, and have been effective, in vivo, in the treatment of sickle cell disease, **radiation exposure**, chemical agent exposure, and other uses.

SUMM **Mesna**, **dimesna**, and analogues thereof are synthesized from commonly available starting materials, using acceptable routes well known in the art. One such method involves the two-step, single pot synthetic process for making **dimesna** and like compounds of the following formula:

SUMM . . . conversion of an alkenyl sulfonate salt or acid to the desired formula I compound. The process in the case of **mesna** is a single step process that converts the alkenyl sulfonate salt to **mesna** or a **mesna** derivative by reacting with an alkali metal sulfide or with hydrogen sulfide.

SUMM If the desired end product is **dimesna** or a **dimesna** analogue, a two-step single pot process is involved. Step 1 is as described above. Step 2 of the process is performed in the same reaction vessel as Step 1 without the need to purify or isolate the **mesna** formed during that step. Step 2 includes the introduction of oxygen gas

into the vessel, along with an increase in pressure and temperature above ambient values, at least 20 pounds per square inch (psi) and at least 60.degree. C. **Dimesna** or a derivative thereof is formed in essentially quantitative yield.

SUMM Other processes, well known and documented in the prior art, may be employed to make either **mesna** or **dimesna**, or derivatives and analogues thereof.

L3 ANSWER 13 OF 27 USPATFULL
AN 2001:33327 USPATFULL
TI Method of treating septic shock
IN Hausheer, Frederick Herman, Boerne, TX, United States
PA BioNumerik Pharmaceuticals, Inc., San Antonio, TX, United States (U.S. corporation)
PI US 6197831 B1 20010306
AI US 1999-247247 19990209 (9)
DT Utility
FS Granted
EXNAM Primary Examiner: Weddington, Kevin E.
LREP Dodd, Thomas J.
CLMN Number of Claims: 4
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 208
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to a method of treating patients afflicted with septic shock. The method includes administering to a patient in need of treatment an effective amount of a thiol or reducible disulfide compound according to the formula set forth in the specification.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM **Mesna** (sodium 2-mercaptoethene sulfonate) and **dimesna** (disodium 2,2'-dithiobis ethane sulfonate) are known therapeutic compounds which have heretofore demonstrated a wide variety of therapeutic uses. Both **mesna** and **dimesna** have been shown to be effective protective agents against certain specific types of toxicity associated with the administration of cytotoxic drugs used to treat patients for various types of cancer. In particular, **mesna** has been used with some success in mitigating the toxic effects of cytotoxic agents such as ifosfamide, oxazaphosphorine, melphalane, cyclophosphamide,. . .

SUMM The near absence of toxicity of **dimesna** further underscores the usefulness of this compound, as large doses that may be needed can be given to a patient. . .

SUMM Further, pharmacological profiles of each compound indicate that, if proper conditions are maintained, **mesna** and **dimesna** do not prematurely inactivate primary therapeutic drugs to a significant degree. Thus, neither compound will significantly reduce activity of the. . .

SUMM The structures of both **mesna** and **dimesna** are shown below as Formula I and Formula II respectively. ##STR1##

SUMM As is well known, **dimesna** is a dimer of **mesna**, with the optimum conditions for oxidation occurring in the slightly basic (pH .about.7.3), oxygen rich environment found in blood plasma.. . . in the presence of a reducing agent such as glutathione reductase, conditions prevalent in the kidneys, the primary constituent is **mesna**.

SUMM **Mesna** acts as a protective agent for a number of cytotoxic agents by substituting a nontoxic sulfhydryl moiety for a toxic hydroxy (or aquo) moiety. This action is particularly evidenced in the coadministration of **mesna** and oxazaphosphorine, and in the administration of **dimesna** along with cisplatin or carboplatin.

SUMM **Mesna** and **dimesna**, as well as some analogues of these compounds, have excellent toxicity profiles in mammalian species. In fact, **dimesna** has been administered intravenously to mice and dogs in doses higher than the accepted oral LD.sub.50 for common table salt (3750 mg/kg), with no adverse effects. **Dimesna** has

also been administered to humans in doses exceeding 15 g/m.sup.2, with no adverse effects.

SUMM **Mesna**, and other analogues with free thiol moieties, constitute the more physiologically active form of the two types of compounds described. . .

SUMM **Dimesna** and other disulfides can be activated intracellularly by glutathione reductase, a ubiquitous enzyme, thereby generating high concentrations of intracellular free. . .

SUMM This profile is especially significant in explaining the success of **dimesna** in controlling and mitigating the toxic effects of platinum complex antitumor drugs. The mechanism for action in the case of. . .

SUMM **Mesna**, **dimesna**, and analogues of these compounds have been the subject of several prior pharmaceutical uses described in the literature and in. . . vitro, against a multiplicity of biological targets, and have been effective, in vivo, in the treatment of sickle cell disease, **radiation exposure**, chemical agent exposure, and other uses.

SUMM **Mesna**, **dimesna**, and analogues thereof are synthesized from commonly available starting materials, using acceptable routes well-known in the art. One such method involves the two-step, single pot synthetic process for making **dimesna** and like compounds of the following formula:

SUMM . . . conversion of an alkenyl sulfonate salt or acid to the desired formula I compound. The process in the case of **mesna** is a single step process which converts the alkenyl sulfonate salt to **mesna** or a **mesna** derivative by reacting with an alkali metal sulfide or with hydrogen sulfide.

SUMM If the desired end product is **dimesna** or a **dimesna** analogue, a two-step single pot process is involved. Step 1 is as described above. Step 2 of the process is performed in the same reaction vessel as Step 1 without the need to purify or isolate the **mesna** formed during that step. Step 2 includes the introduction of oxygen gas into the vessel, along with an increase in pressure and temperature above ambient values, at least 20 pounds per square inch (psi) and at least 60.degree. C. **Dimesna** or a derivative thereof is formed in essentially quantitative yield.

SUMM Other processes, well-known and documented in the prior art, may be employed to make either **mesna** or **dimesna**, or derivatives and analogues thereof.

L3 ANSWER 14 OF 27 USPATFULL
AN 2001:10873 USPATFULL
TI Method for treating heavy metal poisoning
IN Hausheer, Frederick Herman, Boerne, TX, United States
PA BioNumerik Pharmaceuticals, Inc., San Antonio, TX, United States (U.S. corporation)
PI US 6177411 B1 20010123
AI US 1999-247115 19990209 (9)
DT Utility
FS Granted
EXNAM Primary Examiner: Spivack, Phyllis G.
LREP Dodd, Thomas J.
CLMN Number of Claims: 7
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 245
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to a method of treating patients afflicted with heavy metal poisoning. The method includes administering to a patient in need of treatment an antidotal amount of a thiol or reducible disulfide compound according to the formula set forth in the specification.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM **Mesna** (sodium 2-mercaptoethene sulfonate) and **dimesna** (disodium 2,2'-dithiobis ethane sulfonate) are known therapeutic compounds which have heretofore demonstrated a wide variety of

therapeutic uses. Both **mesna** and **dimesna** have been shown to be effective protective agents against certain specific types of toxicity associated with the administration of cytotoxic drugs used to treat patients for various types of cancer. In particular, **mesna** has been used with some success in mitigating the toxic effects of cytotoxic agents such as ifosfamide, oxazaphosphorine, melphalane, cyclophosphamide,. . .

SUMM The near absence of toxicity of **dimesna** further underscores the usefulness of this compound, as large doses that may be needed can be given to a patient. . .

SUMM Further, pharmacological profiles of each compound indicate that, if proper conditions are maintained, **mesna** and **dimesna** do not prematurely inactivate primary therapeutic drugs to a significant degree. Thus, neither compound will significantly reduce activity of the. . .

SUMM The structures of both **mesna** and **dimesna** are shown below as Formula I and Formula II respectively. ##STR1##

SUMM As is well known, **dimesna** is a dimer of **mesna**, with the optimum conditions for oxidation occurring in the slightly basic (pH.about.7.3), oxygen rich environment found in blood plasma. In. . . in the presence of a reducing agent such as glutathione reductase, conditions prevalent in the kidneys, the primary constituent is **mesna**.

SUMM **Mesna** acts as a protective agent for a number of cytotoxic agents by substituting a nontoxic sulfhydryl moiety for a toxic hydroxy (or aquo) moiety. This action is particularly evidenced in the coadministration of **mesna** and oxazaphosphorine, and in the administration of **dimesna** along with cisplatin or carboplatin.

SUMM **Mesna** and **dimesna**, as well as some analogues of these compounds, have excellent toxicity profiles in mammalian species. In fact, **dimesna** has been administered intravenously to mice and dogs in doses higher than the accepted oral LD, for common table salt (3750 mg/kg), with no adverse effects. **Dimesna** has also been administered to humans in doses exceeding 15 g/m.sup.2, with no adverse effects.

SUMM **Mesna**, and other analogues with free thiol moieties, constitute the more physiologically active form of the two types of compounds described. . .

SUMM **Dimesna** and other disulfides can be activated intracellularly by glutathione reductase, a ubiquitous enzyme, thereby generating high concentrations of intracellular free. . .

SUMM This profile is especially significant in explaining the success of **dimesna** in controlling and mitigating the toxic effects of platinum complex antitumor drugs. The mechanism for action in the case of. . .

SUMM **Mesna**, **dimesna**, and analogues of these compounds have been the subject of several prior pharmaceutical uses described in the literature and in. . . vitro, against a multiplicity of biological targets, and have been effective, in vivo, in the treatment of sickle cell disease, **radiation exposure**, chemical agent exposure, and other uses.

SUMM **Mesna**, **dimesna**, and analogues thereof are synthesized from commonly available starting materials, using acceptable routes well-known in the art. One such method involves the two-step, single pot synthetic process for making **dimesna** and like compounds of the following formula:

SUMM . . . conversion of an alkenyl sulfonate salt or acid to the desired formula I compound. The process in the case of **mesna** is a single step process which converts the alkenyl sulfonate salt to **mesna** or a **mesna** derivative by reacting with an alkali metal sulfide or with hydrogen sulfide.

SUMM If the desired end product is **dimesna** or a **dimesna** analogue, two-step single pot process is involved. Step 1 is as described above. Step 2 of the process is performed in the same reaction vessel as Step 1 without the need to purify or isolate the **mesna** formed during that step. Step 2 includes the introduction of oxygen gas into the vessel, along with an increase in pressure and temperature

above ambient values, at least 20 pounds per square inch (psi) and at least 60.degree. C. **Dimesna** or a derivative thereof is formed in essentially quantitative yield.

SUMM Other processes, well-known and documented in the prior art, may be employed to make either **mesna** or **dimesna**, or derivatives and analogues thereof.

L3 ANSWER 15 OF 27 USPATFULL
AN 2001:4793 USPATFULL
TI Method of treating acute renal failure
IN Hausheer, Frederick Herman, Boerne, TX, United States
PA BioNumerik Pharmaceuticals, Inc., San Antonio, TX, United States (U.S. corporation)
PI US 6172119 B1 20010109
AI US 1999-247229 19990209 (9)
DT Patent
FS Granted
EXNAM Primary Examiner: Spivack, Phyllis G.
LREP Dodd, Thomas J.
CLMN Number of Claims: 6
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 224
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to a method of treating patients afflicted with acute renal failure. The method includes administering to a patient in need of treatment an effective amount of a thiol or reducible disulfide compound according to the formula set forth in the specification.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM **Mesna** (sodium 2-mercaptoethene sulfonate) and **dimesna** (disodium 2,2'-dithiobis ethane sulfonate) are known therapeutic compounds which have heretofore demonstrated a wide variety of therapeutic uses. Both **mesna** and **dimesna** have been shown to be effective protective agents against certain specific types of toxicity associated with the administration of cytotoxic drugs used to treat patients for various types of cancer. In particular, **mesna** has been used with some success in mitigating the toxic effects of cytotoxic agents such as ifosfamide, oxazaphosphorine, melphalane, cyclophosphamide,. . .

SUMM The near absence of toxicity of **dimesna** further underscores the usefulness of this compound, as large doses that may be needed can be given to a patient. . .

SUMM Further, pharmacological profiles of each compound indicate that, if proper conditions are maintained, **mesna** and **dimesna** do not prematurely inactivate primary therapeutic drugs to a significant degree. Thus, neither compound will significantly reduce activity of the. . .

SUMM The structures of both **mesna** and **dimesna** are shown below as Formula I and Formula II respectively. ##STR1##

SUMM As is well known, **dimesna** is a dimer of **mesna**, with the optimum conditions for oxidation occurring in the slightly basic (pH.about.7.3), oxygen rich environment found in blood plasma. In. . . in the presence of a reducing agent such as glutathione reductase, conditions prevalent in the kidneys, the primary constituent is **mesna**.

SUMM **Mesna** acts as a protective agent for a number of cytotoxic agents by substituting a nontoxic sulfhydryl moiety for a toxic hydroxy (or aquo) moiety. This action is particularly evidenced in the coadministration of **mesna** and oxazaphosphorine, and in the administration of **dimesna** along with cisplatin or carboplatin.

SUMM **Mesna** and **dimesna**, as well as some analogues of these compounds, have excellent toxicity profiles in mammalian species. In fact, **dimesna** has been administered intravenously to mice and dogs in doses higher than the accepted oral LD.sub.50 for common table salt (3750 mg/kg), with no adverse effects. **Dimesna** has also been administered to humans in doses exceeding 15 g/m.sup.2, with

no adverse effects.

SUMM **Mesna**, and other analogues with free thiol moieties, constitute the more physiologically active form of the two types of compounds described. . .

SUMM **Dimesna** and other disulfides can be activated intracellularly by glutathione reductase, a ubiquitous enzyme, thereby generating high concentrations of intracellular free. . .

SUMM This profile is especially significant in explaining the success of **dimesna** in controlling and mitigating the toxic effects of platinum complex antitumor drugs. The mechanism for action in the case of. . .

SUMM **Mesna**, **dimesna**, and analogues of these compounds have been the subject of several prior pharmaceutical uses described in the literature and in. . . vitro, against a multiplicity of biological targets, and have been effective, in vivo, in the treatment of sickle cell disease, **radiation exposure**, chemical agent exposure, and other uses.

SUMM **Mesna**, **dimesna**, and analogues thereof are synthesized from commonly available starting materials, using acceptable routes well-known in the art. One such method involves the two-step, single pot synthetic process for making **dimesna** and like compounds of the following formula:

SUMM . . . conversion of an alkenyl sulfonate salt or acid to the desired formula I compound. The process in the case of **mesna** is a single step process which converts the alkenyl sulfonate salt to **mesna** or a **mesna** derivative by reacting with an alkali metal sulfide or with hydrogen sulfide.

SUMM If the desired end product is **dimesna** or a **dimesna** analogue, a two-step single pot process is involved. Step 1 is as described above. Step 2 of the process is performed in the same reaction vessel as Step 1 without the need to purify or isolate the **mesna** formed during that step. Step 2 includes the introduction of oxygen gas into the vessel, along with an increase in pressure and temperature above ambient values, at least 20 pounds per square inch (psi) and at least 60.degree. C. **Dimesna** or a derivative thereof is formed in essentially quantitative yield.

SUMM Other processes, well-known and documented in the prior art, may be employed to make either **mesna** or **dimesna**, or derivatives and analogues thereof.

L3 ANSWER 16 OF 27 USPATFULL
AN 2000:150215 USPATFULL
TI Method for reducing development of free radical induced malignancies
IN Hausheer, Frederick H., Boerne, TX, United States
PA BioNumerik Pharmaceuticals, Inc., San Antonio, TX, United States (U.S. corporation)
PI US 6143796 20001107
AI US 1999-389520 19990902 (9)
DT Utility
FS Granted
EXNAM Primary Examiner: Jones, Dwayne C.
LREP Dodd, Thomas J.
CLMN Number of Claims: 4
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 223
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to a method of treating patients at risk of developing a free radical induced malignancy. The method includes administering an effective amount of a thiol or reducible disulfide compound according to the formula set forth in the specification to a patient at risk.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM **Mesna** (sodium 2-mercaptoethene sulfonate) and **dimesna** (disodium 2,2'-dithiobis ethane sulfonate) are known therapeutic compounds which have heretofore demonstrated a wide variety of

therapeutic uses. Both **mesna** and **dimesna** have been shown to be effective protective agents against certain specific types of toxicity associated with the administration of cytotoxic. . .

SUMM In particular, **mesna** has been used with some success in mitigating the toxic effects of cytotoxic agents such as ifosfamide, oxazaphosphorine, melphalane, cyclophosphamide,. . .

SUMM The near absence of toxicity of **dimesna** further underscores the usefulness of this compound, as large doses that may be needed can be given to a patient. . .

SUMM Further, pharmacological profiles of each compound indicate that, if proper conditions are maintained, **mesna** and **dimesna** do not prematurely inactivate primary therapeutic drugs to a significant degree. Thus, neither compound will significantly reduce activity of the. . .

SUMM The structures of both **mesna** and **dimesna** are shown below as Formula A and Formula B respectively. ##STR1##

SUMM As is well known, **dimesna** is a dimer of **mesna**, with the optimum conditions for oxidation occurring in the slightly basic (pH.about.7.3), oxygen rich environment found in blood plasma. In. . . in the presence of a reducing agent such as glutathione reductase, conditions prevalent in the kidneys, the primary constituent is **mesna**.

SUMM **Mesna** acts as a protective agent for a number of cytotoxic agents by substituting a nontoxic sulfhydryl moiety for a toxic hydroxy (or aquo) moiety. This action is particularly evidenced in the coadministration of **mesna** and oxazaphosphorine, and in the administration of **dimesna** along with cisplatin or carboplatin.

SUMM **Mesna** and **dimesna**, as well as some analogues of these compounds, have excellent toxicity profiles in mammalian species. In fact, **dimesna** has been administered intravenously to mice and dogs in doses higher than the accepted oral LD.sub.50 for common table salt (3750 mg/kg), with no adverse effects. **Dimesna** has also been administered to humans in doses exceeding 15 g/m.sup.2, with no adverse effects.

SUMM **Mesna**, and other analogues with free thiol moieties, constitute the more physiologically active form of the two types of compounds described. . .

SUMM **Dimesna** and other disulfides can be activated intracellularly by glutathione reductase, a ubiquitous enzyme, thereby generating high concentrations of intracellular free. . .

SUMM This profile is especially significant in explaining the success of **dimesna** in controlling and mitigating the toxic effects of platinum complex antitumor drugs. The mechanism for action in the case of. . .

SUMM **Mesna**, **dimesna**, and analogues of these compounds have been the subject of several prior pharmaceutical uses described in the literature and in. . . vitro, against a multiplicity of biological targets, and have been effective, in vivo, in the treatment of sickle cell disease, **radiation exposure**, chemical agent exposure, and other uses.

SUMM **Mesna**, **dimesna**, and analogues thereof are synthesized from commonly available starting materials, using acceptable routes well-known in the art. One such method involves the two-step, single pot synthetic process for making **dimesna** and like compounds of the following formula:

SUMM . . . conversion of an alkenyl sulfonate salt or acid to the desired formula I compound. The process in the case of **mesna** is a single step process which converts the alkenyl sulfonate salt to **mesna** or a **mesna** derivative by reacting with an alkali metal sulfide or with hydrogen sulfide.

SUMM If the desired end product is **dimesna** or a **dimesna** analogue, a two-step single pot process is involved. Step 1 is as described above. Step 2 of the process is performed in the same reaction vessel as Step 1 without the need to purify or isolate the **mesna** formed during that step. Step 2 includes the introduction of oxygen gas into the vessel, along with an increase in pressure and temperature above ambient values, at least 20 pounds per square inch (psi) and at

least 60.degree. C. **Dimesna** or a derivative thereof is formed in essentially quantitative yield.

SUMM Other processes, well-known and documented in the prior art, may be employed to make either **mesna** or **dimesna**, or derivatives and analogues thereof.

L3 ANSWER 17 OF 27 USPATFULL
AN 2000:102280 USPATFULL
TI Method of treating diabetic neuropathy
IN Hausheer, Frederick H., Boerne, TX, United States
Parker, Aulma, San Antonio, TX, United States
Peddaiaghari, Seetharamulu, San Antonio, TX, United States
PA BioNumerik Pharmaceuticals, Inc., San Antonio, TX, United States (U.S. corporation)
PI US 6100247 20000808
AI US 1999-422485 19991021 (9)
DT Utility
FS Granted
EXNAM Primary Examiner: Krass, Frederick
LREP Dodd, Thomas J.
CLMN Number of Claims: 4
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 267
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to a method of treating patients afflicted with diabetic neuropathy. The method includes administering to a patient in need of treatment an effective amount of a thiol or reducible disulfide compound according to the formula set forth in the specification.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM **Mesna** (sodium 2-mercaptoethene sulfonate) and **dimesna** (disodium 2,2'-dithiobis ethane sulfonate) are known therapeutic compounds, which have heretofore demonstrated a wide variety of therapeutic uses. Both **mesna** and **dimesna** have been shown to be effective protective agents against certain specific types of toxicity associated with the administration of cytotoxic drugs used to treat patients for various types of cancer. In particular, **mesna** has been used with some success in mitigating the toxic effects of cytotoxic agents such as ifosfamide, oxazaphosphorine, melphalane, cyclophosphamide,. . .

SUMM The near absence of toxicity of **dimesna** further underscores the usefulness of this compound, as large doses that can be given to a patient without increasing the. . .

SUMM Further, pharmacological profiles of each compound indicate that, if proper conditions are maintained, **mesna** and **dimesna** do not prematurely inactivate primary therapeutic drugs to a significant degree. Thus, neither compound will significantly reduce activity of the. . .

SUMM The structures of both **mesna** and **dimesna** are shown below as Formula a and Formula b respectively.

SUMM As is well known, **dimesna** is a dimer of **mesna**, with the optimum conditions for oxidation occurring in the slightly basic (pH .about.7.3), oxygen rich environment found in blood plasma.. . . reducing agent such as glutathione reductase, conditions prevalent in the kidneys, intracellular spaces, intestines, and others, the primary constituent is **mesna**.

SUMM **Mesna** acts as a protective agent for a number of cytotoxic agents by substituting a nontoxic sulfhydryl moiety for a toxic hydroxy (or aquo) moiety. This action is particularly evidenced in the coadministration of **mesna** and oxazaphosphorine, and in the administration of **dimesna** along with cisplatin, carboplatin, and taxane derivatives.

SUMM **Mesna** and **dimesna**, as well as some analogues of these compounds, have excellent toxicity profiles in mammalian species. In fact, **dimesna** has been administered intravenously to mice and dogs in doses higher than the accepted oral LD.sub.50 for common

table salt (3750 mg/kg), with no adverse effects. **Dimesna** has also been administered to humans in doses exceeding 15 g/m.sup.2, with no adverse effects.

SUMM **Mesna**, and other analogues with free thiol moieties, constitute the more physiologically active form of the two types of compounds described. . .

SUMM **Dimesna** and other disulfides can be activated intracellularly by glutathione reductase, a ubiquitous enzyme, thereby generating high concentrations of intracellular free. . .

SUMM This profile is especially significant in explaining the success of **dimesna** in controlling and mitigating the toxic effects of platinum complex antitumor drugs. The mechanism for action in the case of. . .

SUMM **Mesna**, **dimesna**, and analogues of these compounds have been the subject of several prior pharmaceutical uses described in the literature and in. . . vitro, against a multiplicity of biological targets, and have been effective, in vivo, in the treatment of sickle cell disease, **radiation exposure**, chemical agent exposure, and other uses.

SUMM **Mesna**, **dimesna**, and analogues thereof are synthesized from commonly available starting materials, using acceptable routes well known in the art. One such method involves the two-step, single pot synthetic process for making **dimesna** and like compounds of the following formula:

SUMM . . . conversion of an alkenyl sulfonate salt or acid to the desired formula I compound. The process in the case of **mesna** is a single step process, which converts the alkenyl sulfonate salt to **mesna** or a **mesna** derivative by reacting with an alkali metal sulfide or with hydrogen sulfide.

SUMM If the desired end product is **dimesna** or a **dimesna** analogue, a two-step single pot process is involved. Step 1 is as described above. Step 2 of the process is performed in the same reaction vessel as Step 1 without the need to purify or isolate the **mesna** formed during that step. Step 2 includes the introduction of oxygen gas into the vessel, along with an increase in pressure and temperature above ambient values, at least 20 pounds per square inch (psi) and at least 60.degree. C. **Dimesna** or a derivative thereof is formed in essentially quantitative yield.

SUMM Other processes, well known and documented in the prior art, may be employed to make either **mesna** or **dimesna**, or derivatives and analogues thereof.

DETD Briefly, **Dimesna** (0-20 .mu.M) was incubated at 37.degree. C. with aldose reductase (0.0016 units, human recombinant, expressed in SF 9 cells) and. . .

DETD Aldose reductase assays were as described above. **Dimesna** (0-30 mM) was evaluated for its effect on the NADPH dependent reduction of glyceraldehyde (0.050-6 mM) to aldose at 37.degree.. . .

DETD **Dimesna** inhibits aldose reductase catalyzed reduction of glucose to sorbitol and glyceraldehyde to aldose with K.sub.i values of 32 and 15.5. . . Burk plots of the data are nearly parallel and, thus, support an uncompetitive inhibition of the aldose reductase reaction by **Dimesna**. These data suggest that **Dimesna** binds to some form of an enzyme substrate complex. Aldose reductase is a multisubstrate enzyme requiring both NADPH and an aldose sugar for turnover. **Dimesna** binding may be reversible or irreversible.

L3 ANSWER 18 OF 27 USPATFULL
AN 2000:77353 USPATFULL
TI Method of treating hangover
IN Hausheer, Frederick Herman, Boerne, TX, United States
PA BioNumerik Pharmaceuticals, Inc., San Antonio, TX, United States (U.S. corporation)
PI US 6077838 20000620
AI US 1999-327736 19990608 (9)
DT Utility
FS Granted
EXNAM Primary Examiner: Jarvis, William R. A.

LREP Dodd, Thomas J.
CLMN Number of Claims: 4
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 224
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention relates to a method of treating patients afflicted with hangover. The method includes administering to a patient in need of treatment an effective amount of a thiol or reducible disulfide compound according to the formula set forth in the specification.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM **Mesna** (sodium2-mercaptoethane sulfonate) and **dimesna** or (disodium 2,2'-dithiobis ethane sulfonate) are known therapeutic compounds that have heretofore demonstrated a wide variety of therapeutic uses. Both **mesna** and **dimesna** have been shown to be effective protective agents against certain specific types of toxicity associated with the administration of cytotoxic drugs used to treat patients for various types of cancer. In particular, **mesna** has been used with some success in mitigating the toxic effects of cytotoxic agents such as ifosfamide, oxazaphosphorine, melphalane, cyclophosphamide,. . .

SUMM The near absence of toxicity of **dimesna** further underscores the usefulness of this compound, as large doses that may be needed can be given to a patient. . .

SUMM Further, pharmacological profiles of each compound indicate that, if proper conditions are maintained, **mesna** and **dimesna** do not prematurely inactivate primary therapeutic drugs to a significant degree. Thus, neither compound will significantly reduce activity of the. . .

SUMM The structures of both **mesna** and **dimesna** are shown below as Formula I and Formula II respectively. ##STR1##

SUMM As is well known, **dimesna** is a dimer of **mesna**, with the optimum conditions for oxidation occurring in the slightly basic (pH.about.7.3), oxygen rich environment found in blood plasma. In. . . in the presence of a reducing agent such as glutathione reductase, conditions prevalent in the kidneys, the primary constituent is **mesna**.

SUMM **Mesna** acts as a protective agent for a number of cytotoxic agents by substituting a nontoxic sulfhydryl moiety for a toxic hydroxy (or aquo) moiety. This action is particularly evidenced in the coadministration of **mesna** and oxazaphosphorine, and in the administration of **dimesna** along with cisplatin or carboplatin.

SUMM **Mesna** and **dimesna**, as well as some analogues of these compounds, have excellent toxicity profiles in mammalian species. In fact, **dimesna** has been administered intravenously to mice and dogs in doses higher than the accepted oral LD.sub.50 for common table salt (3750 mg/kg), with no adverse effects. **Dimesna** has also been administered to humans in doses exceeding 15 g/m.sup.2, with no adverse effects.

SUMM **Mesna**, and other analogues with free thiol moieties, constitute the more physiologically active form of the two types of compounds described. . .

SUMM **Dimesna** and other disulfides can be activated intracellularly by glutathione reductase, a ubiquitous enzyme, thereby generating high concentrations of intracellular free. . .

SUMM This profile is especially significant in explaining the success of **dimesna** in controlling and mitigating the toxic effects of platinum complex antitumor drugs. The mechanism for action in the case of. . .

SUMM **Mesna**, **dimesna**, and analogues of these compounds have been the subject of several prior pharmaceutical uses described in the literature and in. . . vitro, against a multiplicity of biological targets, and have been effective, in vivo, in the treatment of sickle cell disease, **radiation exposure**, chemical agent exposure, and other uses.

SUMM **Mesna**, **dimesna**, and analogues thereof are

synthesized from commonly available starting materials, using acceptable routes well-known in the art. One such method involves the two-step, single pot synthetic process for making **dimesna** and like compounds of the following formula:

SUMM . . . conversion of an alkenyl sulfonate salt or acid to the desired formula I compound. The process in the case of **mesna** is a single step process that converts the alkenyl sulfonate salt to **mesna** or a **mesna** derivative by reacting with an alkali metal sulfide or with hydrogen sulfide.

SUMM If the desired end product is **dimesna** or a **dimesna** analogue, a two-step single pot process is involved. Step 1 is as described above. Step 2 of the process is performed in the same reaction vessel as Step 1 without the need to purify or isolate the **mesna** formed during that step. Step 2 includes the introduction of oxygen gas into the vessel, along with an increase in pressure and temperature above ambient values, at least 20 pounds per square inch (psi) and at least 60.degree. C. **Dimesna** or a derivative thereof is formed in essentially quantitative yield.

SUMM Other processes, well-known and documented in the prior art, may be employed to make either **mesna** or **dimesna**, or derivatives and analogues thereof.

L3 ANSWER 19 OF 27 USPATFULL
AN 2000:74318 USPATFULL
TI Method of reducing or reversing neuropathy
IN Hausheer, Frederick Herman, Boerne, TX, United States
PA BioNumerik Pharmaceuticals, Inc., San Antonio, TX, United States (U.S. corporation)
PI US 6075053 20000613
AI US 1999-246471 19990209 (9)
DT Utility
FS Granted
EXNAM Primary Examiner: Henley, III, Raymond; Assistant Examiner: Kim, Jennifer
LREP Dodd, Thomas J.
CLMN Number of Claims: 5
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 241
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to a method of treating patients afflicted with peripheral neuropathy. The method includes administering to a patient in need of treatment an effective amount of a thiol or reducible disulfide compound according to the formula set forth in the specification.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM **Mesna** (sodium 2-mercaptoethene sulfonate) and **dimesna** (disodium 2,2'-dithiobis ethane sulfonate) are known therapeutic compounds which have heretofore demonstrated a wide variety of therapeutic uses. Both **mesna** and **dimesna** have been shown to be effective protective agents against certain specific types of toxicity associated with the administration of cytotoxic drugs used to treat patients for various types of cancer. In particular, **mesna** has been used with some success in mitigating the toxic effects of cytotoxic agents such as ifosfamide, oxazaphosphorine, melphalane, cyclophosphamide,. . .

SUMM The near absence of toxicity of **dimesna** further underscores the usefulness of this compound, as large doses that may be needed can be given to a patient. . .

SUMM Further, pharmacological profiles of each compound indicate that, if proper conditions are maintained, **mesna** and **dimesna** do not prematurely inactivate primary therapeutic drugs to a significant degree. Thus, neither compound will significantly reduce activity of the. . .

SUMM The structures of both **mesna** and **dimesna** are shown below as Formula I and Formula II respectively. ##STR1##

SUMM As is well known, **dimesna** is a dimer of **mesna**, with

the optimum conditions for oxidation occurring in the slightly basic (pH .about.7.3), oxygen rich environment found in blood plasma.. . . in the presence of a reducing agent such as glutathione reductase, conditions prevalent in the kidneys, the primary constituent is **mesna**.

SUMM **Mesna** acts as a protective agent for a number of cytotoxic agents by substituting a nontoxic sulfhydryl moiety for a toxic hydroxy (or aquo) moiety. This action is particularly evidenced in the coadministration of **mesna** and oxazaphosphorine, and in the administration of **dimesna** along with cisplatin or carboplatin.

SUMM **Mesna** and **dimesna**, as well as some analogues of these compounds, have excellent toxicity profiles in mammalian species. In fact, **dimesna** has been administered intravenously to mice and dogs in doses higher than the accepted oral LD.sub.50 for common table salt (3750 mg/kg), with no adverse effects. **Dimesna** has also been administered to humans in doses exceeding 15 g/m.sup.2, with no adverse effects.

SUMM **Mesna**, and other analogues with free thiol moieties, constitute the more physiologically active form of the two types of compounds described. . .

SUMM **Dimesna** and other disulfides can be activated intracellularly by glutathione reductase, a ubiquitous enzyme, thereby generating high concentrations of intracellular free. . .

SUMM This profile is especially significant in explaining the success of **dimesna** in controlling and mitigating the toxic effects of platinum complex antitumor drugs. The mechanism for action in the case of. . .

SUMM **Mesna**, **dimesna**, and analogues of these compounds have been the subject of several prior pharmaceutical uses described in the literature and in. . . vitro, against a multiplicity of biological targets, and have been effective, in vivo, in the treatment of sickle cell disease, **radiation exposure**, chemical agent exposure, and other uses.

SUMM **Mesna**, **dimesna**, and analogues thereof are synthesized from commonly available starting materials, using acceptable routes well-known in the art. One such method involves the two-step, single pot synthetic process for making **dimesna** and like compounds of the following formula:

SUMM . . . conversion of an alkenyl sulfonate salt or acid to the desired formula I compound. The process in the case of **mesna** is a single step process which converts the alkenyl sulfonate salt to **mesna** or a **mesna** derivative by reacting with an alkali metal sulfide or with hydrogen sulfide.

SUMM If the desired end product is **dimesna** or a **dimesna** analogue, a two-step single pot process is involved. Step 1 is as described above. Step 2 of the process is performed in the same reaction vessel as Step 1 without the need to purify or isolate the **mesna** formed during that step. Step 2 includes the introduction of oxygen gas into the vessel, along with an increase in pressure and temperature above ambient values, at least 20 pounds per square inch (psi) and at least 60.degree. C. **Dimesna** or a derivative thereof is formed in essentially quantitative yield.

SUMM Other processes, well-known and documented in the prior art, may be employed to make either **mesna** or **dimesna**, or derivatives and analogues thereof.

L3 ANSWER 20 OF 27 USPATFULL
AN 2000:37830 USPATFULL
TI Method of treating diabetic cardiomyopathy
IN Hausheer, Frederick H., Boerne, TX, United States
Parker, Aulma, San Antonio, TX, United States
Peddaiahgari, Seetharamulu, San Antonio, TX, United States
PA BioNumerik Pharmaceuticals, Inc., San Antonio, TX, United States (U.S. corporation)
PI US 6043274 20000328
AI US 1999-422479 19991021 (9)
DT Utility

FS Granted
EXNAM Primary Examiner: Spivack, Phyllis G.
LREP Dodd, Thomas J.
CLMN Number of Claims: 4
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 276
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to a method of treating patients afflicted with diabetic cardiomyopathy. The method includes administering to a patient in need of treatment an effective amount of a thiol or reducible disulfide compound according to the formula set forth in the specification.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM **Mesna** (sodium 2-mercaptoethene sulfonate) and **dimesna** (disodium 2,2'-dithiobis ethane sulfonate) are known therapeutic compounds, which have heretofore demonstrated a wide variety of therapeutic uses. Both **mesna** and **dimesna** have been shown to be effective protective agents against certain specific types of toxicity associated with the administration of cytotoxic drugs used to treat patients for various types of cancer. In particular, **mesna** has been used with some success in mitigating the toxic effects of cytotoxic agents such as ifosfamide, oxazaphosphorine, melphalane, cyclophosphamide,. . .

SUMM The near absence of toxicity of **dimesna** further underscores the usefulness of this compound, as large doses that can be given to a patient without increasing the. . .

SUMM Further, pharmacological profiles of each compound indicate that, if proper conditions are maintained, **mesna** and **dimesna** do not prematurely inactivate primary therapeutic drugs to a significant degree. Thus, neither compound will significantly reduce activity of the. . .

SUMM The structures of both **mesna** and **dimesna** are shown below as Formula a and Formula b respectively.

SUMM As is well known, **dimesna** is a dimer of **mesna**, with the optimum conditions for oxidation occurring in the slightly basic (pH .about.7.3), oxygen rich environment found in blood plasma.. . . reducing agent such as glutathione reductase, conditions prevalent in the kidneys, intracellular spaces, intestines, and others, the primary constituent is **mesna**.

SUMM **Mesna** acts as a protective agent for a number of cytotoxic agents by substituting a nontoxic sulfhydryl moiety for a toxic hydroxy (or aquo) moiety. This action is particularly evidenced in the coadministration of **mesna** and oxazaphosphorine, and in the administration of **dimesna** along with cisplatin, carboplatin, and taxane derivatives.

SUMM **Mesna** and **dimesna**, as well as some analogues of these compounds, have excellent toxicity profiles in mammalian species. In fact, **dimesna** has been administered intravenously to mice and dogs in doses higher than the accepted oral LD.sub.50 for common table salt (3750 mg/kg), with no adverse effects. **Dimesna** has also been administered to humans in doses exceeding 15 g/m.sup.2, with no adverse effects.

SUMM **Mesna**, and other analogues with free thiol moieties, constitute the more physiologically active form of the two types of compounds described. . .

SUMM **Dimesna** and other disulfides can be activated intracellularly by glutathione reductase, a ubiquitous enzyme, thereby generating high concentrations of intracellular free. . .

SUMM This profile is especially significant in explaining the success of **dimesna** in controlling and mitigating the toxic effects of platinum complex antitumor drugs. The mechanism for action in the case of. . .

SUMM **Mesna**, **dimesna**, and analogues of these compounds have been the subject of several prior pharmaceutical uses described in the literature and in. . . vitro, against a multiplicity of

biological targets, and have been effective, in vivo, in the treatment of sickle cell disease, **radiation exposure**, chemical agent exposure, and other uses.

SUMM **Mesna**, **dimesna**, and analogues thereof are synthesized from commonly available starting materials, using acceptable routes well known in the art. One such method involves the two-step, single pot synthetic process for making **dimesna** and like compounds of the following formula:

SUMM . . . conversion of an alkenyl sulfonate salt or acid to the desired formula I compound. The process in the case of **mesna** is a single step process, which converts the alkenyl sulfonate salt to **mesna** or a **mesna** derivative by reacting with an alkali metal sulfide or with hydrogen sulfide.

SUMM If the desired end product is **dimesna** or a **dimesna** analogue, a two-step single pot process is involved. Step 1 is as described above. Step 2 of the process is performed in the same reaction vessel as Step 1 without the need to purify or isolate the **mesna** formed during that step. Step 2 includes the introduction of oxygen gas into the vessel, along with an increase in pressure and temperature above ambient values, at least 20 pounds per square inch (psi) and at least 60.degree. C. **Dimesna** or a derivative thereof is formed in essentially quantitative yield.

SUMM Other processes, well known and documented in the prior art, may be employed to make either **mesna** or **dimesna**, or derivatives and analogues thereof.

DETD Briefly, **Dimesna** (0-20 .mu.M) was incubated at 37.degree. C. with aldose reductase (0.0016 units, human recombinant, expressed in SF 9 cells) and. . .

DETD Aldose reductase assays were as described above. **Dimesna** (0-30 mM) was evaluated for its effect on the NADPH dependent reduction of glyceraldehyde (0.050-6 mM) to aldose at 37.degree.. . .

L3 ANSWER 21 OF 27 USPATFULL

AN 2000:28022 USPATFULL

TI Method for treating glycol poisoning

IN Hausheer, Frederick Herman, Boerne, TX, United States

PA BioNumerik Pharmaceuticals, Inc., San Antonio, TX, United States (U.S. corporation)

PI US 6034126 20000307

AI US 1999-317693 19990524 (9)

DT Utility

FS Granted

EXNAM Primary Examiner: Spivack, Phyllis G.

LREP Dodd, Thomas J.

CLMN Number of Claims: 6

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 244

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention relates to a method of treating patients afflicted with glycol poisoning. The method includes administering to a patient in need of treatment an antidotal amount of a thiol or reducible disulfide compound according to the formula set forth in the specification.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM **Mesna** (sodium 2-mercaptoethene sulfonate) and **dimesna** (disodium 2,2'-dithiobis ethane sulfonate) are known therapeutic compounds which have heretofore demonstrated a wide variety of therapeutic uses. Both **mesna** and **dimesna** have been shown to be effective protective agents against certain specific types of toxicity associated with the administration of cytotoxic drugs used to treat patients for various types of cancer. In particular, **mesna** has been used with some success in mitigating the toxic effects of cytotoxic agents such as ifosfamide, oxazaphosphorine, melphalane, cyclophosphamide,. . .

SUMM The near absence of toxicity of **dimesna** further underscores the usefulness of this compound, as large doses that may be needed can

be given to a patient. . .

SUMM Further, pharmacological profiles of each compound indicate that, if proper conditions are maintained, **mesna** and **dimesna** do not prematurely inactivate primary therapeutic drugs to a significant degree. Thus, neither compound will significantly reduce activity of the. . .

SUMM The structures of both **mesna** and **dimesna** are shown below as Formula I and Formula II respectively. ##STR1##

SUMM As is well known, **dimesna** is a dimer of **mesna**, with the optimum conditions for oxidation occurring in the slightly basic (pH .about.7.3), oxygen rich environment found in blood plasma.. . . in the presence of a reducing agent such as glutathione reductase, conditions prevalent in the kidneys, the primary constituent is **mesna**.

SUMM **Mesna** acts as a protective agent for a number of cytotoxic agents by substituting a nontoxic sulfhydryl moiety for a toxic hydroxy (or aquo) moiety. This action is particularly evidenced in the coadministration of **mesna** and oxazaphosphorine, and in the administration of **dimesna** along with cisplatin or carboplatin.

SUMM **Mesna** and **dimesna**, as well as some analogues of these compounds, have excellent toxicity profiles in mammalian species. In fact, **dimesna** has been administered intravenously to rats and dogs in doses higher than the accepted oral LD.sub.50 for common table salt (3750 mg/kg), with no adverse effects. **Dimesna** has also been administered to humans in doses exceeding 25 g/m.sup.2 with no adverse effects.

SUMM **Mesna**, and other analogues with free thiol moieties, constitute the more physiologically active form of the two types of compounds described. . .

SUMM **Dimesna** and other disulfides can be activated intracellularly by glutathione reductase, a ubiquitous enzyme, thereby generating high concentrations of intracellular free. . .

SUMM This profile is especially significant in explaining the success of **dimesna** in controlling and mitigating the toxic effects of platinum complex antitumor drugs. The mechanism for action in the case of. . .

SUMM **Mesna**, **dimesna**, and analogues of these compounds have been the subject of several prior pharmaceutical uses described in the literature and in. . . vitro, against a multiplicity of biological targets, and have been effective, in vivo, in the treatment of sickle cell disease, **radiation exposure**, chemical agent exposure, and other uses.

SUMM **Mesna**, **dimesna**, and analogues thereof are synthesized from commonly available starting materials, using acceptable routes well-known in the art. One such method involves the two-step, single pot synthetic process for making **dimesna** and like compounds of the following formula:

SUMM . . . conversion of an alkenyl sulfonate salt or acid to the desired formula I compound. The process in the case of **mesna** is a single step process which converts the alkenyl sulfonate salt to **mesna** or a **mesna** derivative by reacting with an alkali metal sulfide or with hydrogen sulfide.

SUMM If the desired end product is **dimesna** or a **dimesna** analogue, a two-step single pot process is involved. Step 1 is as described above. Step 2 of the process is performed in the same reaction vessel as Step 1 without the need to purify or isolate the **mesna** formed during that step. Step 2 includes the introduction of oxygen gas into the vessel, along with an increase in pressure and temperature above ambient values, at least 20 pounds per square inch (psi) and at least 60.degree. C. **Dimesna** or a derivative thereof is formed in essentially quantitative yield.

SUMM Other processes, well-known and documented in the prior art, may be employed to make either **mesna** or **dimesna**, or derivatives and analogues thereof.

L3 ANSWER 22 OF 27 USPATFULL
AN 2000:24680 USPATFULL

TI Method of treating diabetic nephropathy
IN Hausheer, Frederick H., Boerne, TX, United States
Parker, Aulma, San Antonio, TX, United States
Peddaiaghari, Seetharamulu, San Antonio, TX, United States
PA BioNumerik Pharmaceuticals, Inc., San Antonio, TX, United States (U.S. corporation)
PI US 6031006 20000229
AI US 1999-422486 19991021 (9)
DT Utility
FS Granted
EXNAM Primary Examiner: Henley, III, Raymond
LREP Dodd, Thomas J.
CLMN Number of Claims: 4
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 271
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to a method of treating patients afflicted with diabetic nephropathy. The method includes administering to a patient in need of treatment an effective amount of a thiol or reducible disulfide compound according to the formula set forth in the specification.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM **Mesna** (sodium 2-mercaptoethene sulfonate) and **dimesna** (disodium 2,2'-dithiobis ethane sulfonate) are known therapeutic compounds, which have heretofore demonstrated a wide variety of therapeutic uses. Both **mesna** and **dimesna** have been shown to be effective protective agents against certain specific types of toxicity associated with the administration of cytotoxic drugs used to treat patients for various types of cancer. In particular, **mesna** has been used with some success in mitigating the toxic effects of cytotoxic agents such as ifosfamide, oxazaphosphorine, melphalane, cyclophosphamide,. . .
SUMM The near absence of toxicity of **dimesna** further underscores the usefulness of this compound, as large doses that can be given to a patient without increasing the. . .
SUMM Further, pharmacological profiles of each compound indicate that, if proper conditions are maintained, **mesna** and **dimesna** do not prematurely inactivate primary therapeutic drugs to a significant degree. Thus, neither compound will significantly reduce activity of the. . .
SUMM The structures of both **mesna** and **dimesna** are shown below as Formula a and Formula b respectively.
SUMM As is well known, **dimesna** is a dimer of **mesna**, with the optimum conditions for oxidation occurring in the slightly basic (pH .about.7.3), oxygen rich environment found in blood plasma.. . . reducing agent such as glutathione reductase, conditions prevalent in the kidneys, intracellular spaces, intestines, and others, the primary constituent is **mesna**.
SUMM **Mesna** acts as a protective agent for a number of cytotoxic agents by substituting a nontoxic sulfhydryl moiety for a toxic hydroxy (or aquo) moiety. This action is particularly evidenced in the coadministration of **mesna** and oxazaphosphorine, and in the administration of **dimesna** along with cisplatin, carboplatin, and taxane derivatives.
SUMM **Mesna** and **dimesna**, as well as some analogues of these compounds, have excellent toxicity profiles in mammalian species. In fact, **dimesna** has been administered intravenously to mice and dogs in doses higher than the accepted oral LD.sub.50 for common table salt (3750 mg/kg), with no adverse effects. **Dimesna** has also been administered to humans in doses exceeding 15 g/m.sup.2, with no adverse effects.
SUMM **Mesna**, and other analogues with free thiol moieties, constitute the more physiologically active form of the two types of compounds described. . .
SUMM **Dimesna** and other disulfides can be activated intracellularly by glutathione reductase, a ubiquitous enzyme, thereby generating high

concentrations of intracellular free. . .

SUMM This profile is especially significant in explaining the success of **dimesna** in controlling and mitigating the toxic effects of platinum complex antitumor drugs. The mechanism for action in the case of. . .

SUMM **Mesna**, **dimesna**, and analogues of these compounds have been the subject of several prior pharmaceutical uses described in the literature and in. . . vitro, against a multiplicity of biological targets, and have been effective, in vivo, in the treatment of sickle cell disease, **radiation exposure**, chemical agent exposure, and other uses.

SUMM **Mesna**, **dimesna**, and analogues thereof are synthesized from commonly available starting materials, using acceptable routes well known in the art. One such method involves the two-step, single pot synthetic process for making **dimesna** and like compounds of the following formula:

SUMM . . . conversion of an alkenyl sulfonate salt or acid to the desired formula I compound. The process in the case of **mesna** is a single step process, which converts the alkenyl sulfonate salt to **mesna** or a **mesna** derivative by reacting with an alkali metal sulfide or with hydrogen sulfide.

SUMM If the desired end product is **dimesna** or a **dimesna** analogue, a two-step single pot process is involved. Step 1 is as described above. Step 2 of the process is performed in the same reaction vessel as Step 1 without the need to purify or isolate the **mesna** formed during that step. Step 2 includes the introduction of oxygen gas into the vessel, along with an increase in pressure and temperature above ambient values, at least 20 pounds per square inch (psi) and at least 60.degree. C. **Dimesna** or a derivative thereof is formed in essentially quantitative yield.

SUMM Other processes, well known and documented in the prior art, may be employed to make either **mesna** or **dimesna**, or derivatives and analogues thereof.

DETD Briefly, **Dimesna** (0-20 .mu.M) was incubated at 37.degree. C. with aldose reductase (0.0016 units, human recombinant, expressed in SF 9 cells) and. . .

DETD Aldose reductase assays were as described above. **Dimesna** (0-30 mM) was evaluated for its effect on the NADPH dependent reduction of glyceraldehyde (0.050-6 mM) to aldose at 37.degree.. . .

DETD As shown in the above tables, **Dimesna** inhibits aldose reductase catalyzed reduction of glucose to sorbitol and glyceraldehyde to aldose with K.sub.i values of 32 and 15.5. . . Burk plots of the data are nearly parallel and, thus, support an uncompetitive inhibition of the aldose reductase reaction by **Dimesna**. These data suggest that **Dimesna** binds to some form of an enzyme substrate complex. Aldose reductase is a multisubstrate enzyme requiring both NADPH and an aldose sugar for turnover. **Dimesna** binding may be reversible or irreversible.

L3 ANSWER 23 OF 27 USPATFULL

AN 1999:160095 USPATFULL

TI Method of treating adult respiratory syndrome

IN Hausheer, Frederick Herman, Boerne, TX, United States

PA BioNumerik Pharmaceuticals, Inc., San Antonio, TX, United States (U.S. corporation)

PI US 5998479 19991207

AI US 1999-246476 19990209 (9)

DT Utility

FS Granted

EXNAM Primary Examiner: Spivack, Phyllis G.

LREP Dodd, Thomas J.

CLMN Number of Claims: 5

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 230

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention relates to a method of treating patients afflicted with

Adult Respiratory Distress Syndrome (ARDS). The method includes administering to a patient in need of treatment an effective amount of a thiol or reducible disulfide compound according to the formula set forth in the specification.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM **Mesna** (sodium 2-mercaptoethene sulfonate) and **dimesna** (disodium 2,2'-dithiobis ethane sulfonate) are known therapeutic compounds which have heretofore demonstrated a wide variety of no therapeutic uses. Both **mesna** and **dimesna** have been shown to be effective protective agents against certain specific types of toxicity associated with the administration of cytotoxic drugs used to treat patients for various types of cancer. In particular, **mesna** has been used with some success in mitigating the toxic effects of cytotoxic agents such as ifosfamide, oxazaphosphorine, melphalane, cyclophosphamide,. . .

SUMM The near absence of toxicity of **dimesna** further underscores the usefulness of this compound, as large doses that may be needed can be given to a patient. . .

SUMM Further, pharmacological profiles of each compound indicate that, if proper conditions are maintained, **mesna** and **dimesna** do not prematurely inactivate primary therapeutic drugs to a significant degree. Thus, neither compound will significantly reduce activity of the. . .

SUMM The structures of both **mesna** and **dimesna** are shown below as Formula I and Formula II respectively. ##STR1##

SUMM As is well known, **dimesna** is a dimer of **mesna**, with the optimum conditions for oxidation occurring in the slightly basic (pH .about.7.3), oxygen rich environment found in blood plasma.. . . in the presence of a reducing agent such as glutathione reductase, conditions prevalent in the kidneys, the primary constituent is **mesna**.

SUMM **Mesna** acts as a protective agent for a number of cytotoxic agents by substituting a nontoxic sulfhydryl moiety for a toxic hydroxy (or aquo) moiety. This action is particularly evidenced in the coadministration of **mesna** and oxazaphosphorine, and in the administration of **dimesna** along with cisplatin or carboplatin.

SUMM **Mesna** and **dimesna**, as well as some analogues of these compounds, have excellent toxicity profiles in mammalian species. In fact, **dimesna** has been administered intravenously to mice and dogs in doses higher than the accepted oral LD.sub.50 for common table salt (3750 mg/kg), with no adverse effects. **Dimesna** has also been administered to humans in doses exceeding 15 g/m.sup.2, with no adverse effects.

SUMM **Mesna**, and other analogues with free thiol moieties, constitute the more physiologically active form of the two types of compounds described. . .

SUMM **Dimesna** and other disulfides can be activated intracellularly by glutathione reductase, a ubiquitous enzyme, thereby generating high concentrations of intracellular free. . .

SUMM This profile is especially significant in explaining the success of **dimesna** in controlling and mitigating the toxic effects of platinum complex antitumor drugs. The mechanism for action in the case of. . .

SUMM **Mesna**, **dimesna**, and analogues of these compounds have been the subject of several prior pharmaceutical uses described in the literature and in. . . vitro, against a multiplicity of biological targets, and have been effective, in vivo, in the treatment of sickle cell disease, **radiation exposure**, chemical agent exposure, and other uses.

SUMM **Mesna**, **dimesna**, and analogues thereof are synthesized from commonly available starting materials, using acceptable routes well-known in the art. One such method involves the two-step, single pot synthetic process for making **dimesna** and like compounds of the following formula:

SUMM . . . conversion of an alkenyl sulfonate salt or acid to the desired formula I compound. The process in the case of **mesna** is a

single step process which converts the alkenyl sulfonate salt to **mesna** or a **mesna** derivative by reacting with an alkali metal sulfide or with hydrogen sulfide.

SUMM If the desired end product is **dimesna** or a **dimesna** analogue, a two-step single pot process is involved. Step 1 is as described above. Step 2 of the process is performed in the same reaction vessel as Step 1 without the need to purify or isolate the **mesna** formed during that step. Step 2 includes the introduction of oxygen gas into the vessel, along with an increase in pressure and temperature above ambient values, at least 20 pounds per square inch (psi) and at least 600.degree. C. **Dimesna** or a derivative thereof is formed in essentially quantitative yield.

SUMM Other processes, well-known and documented in the prior art, may be employed to make either **mesna** or **dimesna**, or derivatives and analogues thereof.

L3 ANSWER 24 OF 27 USPATFULL

AN 1998:115714 USPATFULL

TI Pharmaceutical dipeptide compositions and methods of use thereof: immunodepressants

IN Khavinson, Vladimir Kh., St. Petersburg, Russian Federation
Morozov, Vyacheslav G., St. Petersburg, Russian Federation

PA Cytran, Inc., Kirkland, WA, United States (U.S. corporation)

PI US 5811399 19980922

AI US 4509048 19950526 (8)

RLI Continuation-in-part of Ser. No. 278463, filed on 21 Jul 1994, now abandoned And Ser. No. 337341, filed on 10 Nov 1994, now patented, Pat. No. 5538951 which is a continuation-in-part of Ser. No. 257495, filed on 7 Jun 1994, now abandoned which is a continuation of Ser. No. 783518, filed on 28 Oct 1991, now abandoned which is a continuation-in-part of Ser. No. 678129, filed on 1 Apr 1991, now abandoned which is a continuation-in-part of Ser. No. 415283, filed on 30 Aug 1989, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Tsang, Cecilia J.; Assistant Examiner: Harle, Jennifer

CLMN Number of Claims: 12

ECL Exemplary Claim: 1

DRWN 14 Drawing Figure(s); 7 Drawing Page(s)

LN.CNT 8863

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods of treatment of subjects for decreasing cell mediated autoimmunity or humoral autoimmunity by administering an R'-Glu-Trp-R" pharmaceutical preparation useful in subjects having autoimmune diseases.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . so useful include: chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine hydrochloride, melphalan, thiotepa, busulfan, procarbazine hydrochloride, carmustine, lomustine, streptozocin, cisplatin, carboplatin, dacarbazine, altretamine, **mesna**, methotrexate, leucovorin calcium, cytarabine, floxuridine, fluorouracil, cladribine, fludarabine, mercaptopurine, pentostatin, thioguanine, hydroxyurea, bleomycin sulfate, dactinomycin, daunorubicin hydrochloride, doxorubicin hydrochloride, idarubicin. . .

DETD . . . and patients with thoracic cavity tumors and other cancers after radiation therapy (EXAMPLE 3, Protocols A-C); ii) patients having occupational **radiation exposure** (EXAMPLE 12, Protocols A and B); and, iii) patients following adult thymectomy EXAMPLE 24). Illustrative examples of other immunocompromised patients. . .

DETD . . . World J. Surgery 16(5): 918-923 (1992)). Hematological data have also been used to construct an empirical dose curve for gamma **radiation exposure** at Chernobyl and values reported for 127 of the former residents range from 0.5 Gy to 12 Gy (Konchalovskii, M.. . .

DETD Approximately 120,000 former Chernobyl residents are currently

reportedly being followed to determine long term effects of **radiation exposure**. In patients suffering from acute radiation sickness during the accident, immune defects have been reported three to five years later. . .

DETD . . . and T- and B-lymphocyte populations were determined using a flow cytometer and monoclonal antibodies specific for lymphocyte cell surface markers. **Radiation exposure** levels for the different patients were determined using dosimetry data obtained by the military in Chernobyl using a D-2-P dosimeter.. . .

DETD . . . 2 that a response to the Thymalin treatment was observed in the treatment population even at this early time after **radiation exposure** in Chernobyl.

DETD TABLE 2

Thymalin Treatment of Chernobyl Subjects (X .+-. m):
Treatments Initiated Shortly after Accidental **Radiation Exposure**

Laboratory Indicia.sup.a	Examination Group: Healthy Normal Controls	Accidental **Radiation Exposure**: Before	After Thymalin
Leukocytes, abs	5.7 .+-. 0.3	3.8 .+-. 0.3*	6.4 .+-. 0.8**
% Normal Value:	(100%)	(67%)	(112%)

Ratio Post-/Pre-Treat.sup.b. . .

DETD TABLE 3

Treatment of Radiation-Induced Immunodeficiency: Treatments with Thymalin at Two Months Post-**Radiation Exposure** (X .+-. m)

Indicia.sup.a	Examination Group: Healthy Normal Control	Accidental Irradiation: Before	After Thymalin Treatment
Leukocytes, abs	5.6 .+-. 0.8	3.5 .+-.. . .	

DETD . . . occur in subjects exposed to radiation, presumably because of decreased immune surveillance and elimination of tumor cells. At three years post-**radiation exposure**, preliminary evaluation of patients exposed to radiation at Chernobyl suggested lingering impaired immunity in 20% of the subjects as evidenced. . .

DETD TABLE 6

Indices of Cellular Immunity and Innate Immunity in Chernobyl Subject Receiving Treatment
with L--Glu--L--Trp at 3 Years Post-**Radiation Exposure**

Laboratory Test Results: Before Indicia Therapy	After: Untreated	L--Glu--L--Trp
Leukocytes,	5.8 .+-. 0.3	5.5 .+-. 1.0
abs Lympho-	2.0 .+-. 0.3	1.8 .+-.. . .

DETD Occupational **Radiation Exposure**

DETD . . . in anti-bacterial, anti-viral, and anti-parasitic immunity. The

levels of lymphocytes in thymus, spleen, and lymph node are decreased following sub-lethal **radiation exposure**, and the effects of L--Glu--L--Trp on recovery of immune function following **radiation exposure** were investigated in this model.

L3 ANSWER 25 OF 27 USPATFULL
AN 1998:111911 USPATFULL
TI Method for treatment of purulent inflammatory diseases
IN Morozov, Vyacheslav G., St. Petersburg, Russian Federation
Khavinson, Vladimir Kh., St. Petersburg, Russian Federation
PA Cytoven J.V., Kirkland, WA, United States (U.S. corporation)
PI US 5807830 19980915
AI US 1995-452061 19950526 (8)
RLI Continuation-in-part of Ser. No. US 1994-337341, filed on 10 Nov 1994, now patented, Pat. No. US 5538951 And a continuation-in-part of Ser. No. US 1994-278463, filed on 21 Jul 1994, now abandoned which is a continuation-in-part of Ser. No. US 1994-257495, filed on 7 Jun 1994, now abandoned which is a continuation of Ser. No. US 1991-783518, filed on 28 Oct 1991, now abandoned which is a continuation-in-part of Ser. No. US 1991-678129, filed on 1 Apr 1991, now abandoned which is a continuation-in-part of Ser. No. US 1989-415283, filed on 30 Aug 1989, now abandoned
PRAI SU 1987-4352833 19871230
DT Utility
FS Granted
EXNAM Primary Examiner: Jones, W. Gary; Assistant Examiner: Fredman, Jeffrey
CLMN Number of Claims: 11
ECL Exemplary Claim: 1
DRWN 16 Drawing Figure(s); 8 Drawing Page(s)
LN.CNT 8879
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention provides methods of treating purulent inflammatory diseases by administering L-Glu-L-Trp or a salt thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD . . . so useful include: chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine hydrochloride, melphalan, thiotepa, busulfan, procarbazine hydrochloride, carmustine, lomustine, streptozocin, cisplatin, carboplatin, dacarbazine, altretamine, **mesna**, methotrexate, leucovorin calcium, cytarabine, floxuridine, fluorouracil, cladribine, fludarabine, mercaptopurine, pentostatin, thioguanine, hydroxyurea, bleomycin sulfate, dactinomycin, daunorubicin hydrochloride, doxorubicin hydrochloride, idarubicin. . .
DETD . . . and patients with thoracic cavity tumors and other cancers after radiation therapy (EXAMPLE 3, Protocols A-C); ii) patients having occupational **radiation exposure** (EXAMPLE 12, Protocols A and B); and, iii) patients following adult thymectomy (EXAMPLE 24). Illustrative examples of other immunocompromised patients. . .
DETD . . . World J. Surgery 16(5): 918-923 (1992)). Hematological data have also been used to construct an empirical dose curve for gamma **radiation exposure** at Chernobyl and values reported for 127 of the former residents range from 0.5 Gy to 12 Gy (Konchalovskii, M.. . .
DETD Approximately 120,000 former Chernobyl residents are currently reportedly being followed to determine long term effects of **radiation exposure**. In patients suffering from acute radiation sickness during the accident, immune defects have been reported three to five years later. . .
DETD . . . and T- and B-lymphocyte populations were determined using a flow cytometer and monoclonal antibodies specific for lymphocyte cell surface markers. **Radiation exposure** levels for the different patients were determined using dosimetry data obtained by the military in Chernobyl using a D-2-P dosimeter.. . .
DETD . . . 2 that a response to the Thymalin treatment was observed in the treatment population even at this early time after **radiation exposure** in Chernobyl.

DETD TABLE 2

Thymalin Treatment of Chernobyl Subjects (X .+-. m):
Treatments Initiated Shortly after Accidental **Radiation Exposure**

Laboratory Indicia.sup.a	Examination Group: Healthy Normal Controls	Accidental **Radiation Exposure**: Before	After Thymalin
Leukocytes, abs	5.7 .+-. 0.3	3.8 .+-. 0.3*	6.4 .+-. 0.8**
% Normal Value:	(100%)	(67%)	(112%)
Ratio Post-/Pre-. . .			

DETD TABLE 3

Treatment of Radiation-Induced Immunodeficiency:
Treatments with Thymalin at Two Months Post-**Radiation Exposure** (X .+-. m)

Indicia.sup.a	Examination Group: Healthy Normal Controls	Accidental Irradiation: Before	After Thymalin Treatment
Leukocytes, abs	5.6 .+-. 0.8	3.5 .+-.. . .	

DETD . . . occur in subjects exposed to radiation, presumably because of decreased immune surveillance and elimination of tumor cells. At three years post-**radiation exposure**, preliminary evaluation of patients exposed to radiation at Chernobyl suggested lingering impaired immunity in 20% of the subjects as evidenced. . .

DETD TABLE 6

Indices of Cellular Immunity and Innate Immunity in Chernobyl Subject Receiving Treatment with L-Glu-L-Trp at 3 Years Post-**Radiation Exposure**

Indicia	Therapy	Laboratory Test Results: Before	After
	Untreated	L-Glu-L-Trp	
Leukocytes, abs	5.8 .+-. 0.3	5.5 .+-. 1.0	5.6 .+-. 0.4
Lymphocytes; abs	2.0. . .		

DETD Occupational **Radiation Exposure**

DETD . . . in anti-bacterial, anti-viral, and anti-parasitic immunity. The levels of lymphocytes in thymus, spleen, and lymph node are decreased following sub-lethal **radiation exposure**, and the effects of L-Glu-L-Trp on recovery of immune function following **radiation exposure** were investigated in this model.

L3 ANSWER 26 OF 27 USPATFULL
AN 1998:72601 USPATFULL
TI Pharmaceutical dipeptide compositions and methods of use thereof: systemic toxicity
IN Morozov, Vyacheslav G., St. Petersburg, Russian Federation
Khavinson, Vladimir Kh., St. Petersburg, Russian Federation
PA Cytran, Inc., Kirkland, WA, United States (U.S. corporation)
PI US 5770576 19980623

AI US 1995-452077 19950526 (8)
RLI Continuation of Ser. No. US 1994-337341, filed on 10 Nov 1994, now patented, Pat. No. US 5538951 which is a division of Ser. No. US 1989-415283, filed on 30 Aug 1989 And a continuation-in-part of Ser. No. US 1994-278463, filed on 21 Jul 1994, now abandoned which is a continuation-in-part of Ser. No. US 1994-257495, filed on 7 Jun 1994, now abandoned which is a continuation of Ser. No. US 1991-783518, filed on 28 Oct 1991, now abandoned which is a continuation-in-part of Ser. No. US 1991-678129, filed on 1 Apr 1991, now abandoned which is a continuation-in-part of Ser. No. US 1989-415283, filed on 30 Aug 1989, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Robinson, Douglas W.; Assistant Examiner: Harle, Jennifer
CLMN Number of Claims: 13
ECL Exemplary Claim: 1
DRWN 14 Drawing Figure(s); 7 Drawing Page(s)
LN.CNT 8823
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Methods of treatment of subjects with systemic toxicity by administering an R'-Glu-Trp-R" pharmaceutical preparation.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD . . . so useful include: chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine hydrochloride, melphalan, thiotepa, busulfan, procarbazine hydrochloride, carmustine, lomustine, streptozocin, cisplatin, carboplatin, dacarbazine, altretamine, **mesna**, methotrexate, leucovorin calcium, cytarabine, floxuridine, fluorouracil, cladribine, fludarabine, mercaptopurine, pentostatin, thioguanine, hydroxyurea, bleomycin sulfate, dactinomycin, daunorubicin hydrochloride, doxorubicin hydrochloride, idarubicin. . .
DETD . . . and patients with thoracic cavity tumors and other cancers after radiation therapy (EXAMPLE 3, Protocols A-C); ii) patients having occupational **radiation exposure** (EXAMPLE 12, Protocols A and B); and, iii) patients following adult thymectomy (EXAMPLE 24). Illustrative examples of other immunocompromised patients. . .
DETD . . . World J. Surgery 16(5): 918-923 (1992)). Hematological data have also been used to construct an empirical dose curve for gamma **radiation exposure** at Chernobyl and values reported for 127 of the former residents range from 0.5 Gy to 12 Gy. (Konchalovskii, M.. . .
DETD Approximately 120,000 former Chernobyl residents are currently reportedly being followed to determine long term effects of **radiation exposure**. In patients suffering from acute radiation sickness during the accident, immune defects have been reported three to five years later. . .
DETD . . . and T- and B-lymphocyte populations were determined using a flow cytometer and monoclonal antibodies specific for lymphocyte cell surface markers. **Radiation exposure** levels for the different patients were determined using dosimetry data obtained by the military in Chernobyl using a D-2-P dosimeter.. . .
DETD . . . 2 that a response to the Thymalin treatment was observed in the treatment population even at this early time after **radiation exposure** in Chernobyl.
DETD TABLE 2

Thymalin Treatment of Chernobyl Subjects (X .+-. m):
Treatments Initiated Shortly after Accidental **Radiation Exposure**

Examination Group			
Healthy			
Laboratory	Normal	Accidental **Radiation Exposure**	
Indicia.sup.a			
	Controls	Before	After Thymalin

Leukocytes, abs
5.7 .+-. 0.3
3.8 .+-. 0.3*
6.41 .+-. 0.8**
% Normal Value:
(100%) (67%) (112%)
Ratio Post-/Pre-Treat.sup.b. . .
DETD TABLE 3

Treatment of Radiation-Induced Immunodeficiency:
Treatments with Thymalin at Two Months Post-**Radiation Exposure**(X .+-. m)
Examination Group
Healthy Accidental Irradiation
Normal After Thymalin
Indicia.sup.a
Control Before Treatment

Leukocytes, abs
5.6 .+-. 0.8
3.5 .+-. 0.4*
. . .
DETD . . . occur in subjects exposed to radiation, presumably because of decreased immune surveillance and elimination of tumor cells. At three years post-**radiation exposure**, preliminary evaluation of patients exposed to radiation at Chernobyl suggested lingering impaired immunity in 20% of the subjects as evidenced. . .
DETD TABLE 6

Indices of Cellular Immunity and Innate Immunity
in Chernobyl Subject Receiving Treatment with
L-Glu-L-Trp at 3 Years Post-**Radiation Exposure**
Laboratory Test Results
Before After
Indicia Therapy Untreated L-Glu-L-Trp

Leukocytes,
5.8 .+-. 0.3
5.5 .+-. 1.0
5.6 .+-. 0.4
abs
Lymphocytes,
2.0 .+-. 0.3
. . .
DETD Occupational **Radiation Exposure**
DETD . . . in anti-bacterial, anti-viral, and anti-parasitic immunity. The levels of lymphocytes in thymus, spleen, and lymph node are decreased following sub-lethal **radiation exposure**, and the effects of L-Glu-L-Trp on recovery of immune function following **radiation exposure** were investigated in this model. 142 guinea pigs were exposed to 1 Gy of X-irradiation and then treated with L-Glu-L-Trp. . .

L3 ANSWER 27 OF 27 USPATFULL
AN 1998:28061 USPATFULL
TI Methods for normalizing numbers of lymphocytes
IN Morozov, Vyacheslav G., St. Petersburg, Russian Federation
Khavinson, Vladimir Kh., St. Petersburg, Russian Federation
PA Cytoven J.V., Kirkland, WA, United States (U.S. corporation)
PI US 5728680 19980317
AI US 1995-452411 19950526 (8)
RLI Continuation-in-part of Ser. No. US 1994-337341, filed on 10 Nov 1994, now patented, Pat. No. US 5538951 And a continuation-in-part of Ser. No. US 1994-278463, filed on 21 Jul 1994, now abandoned which is a continuation-in-part of Ser. No. US 1994-257495, filed on 7 Jun 1994, now abandoned which is a continuation of Ser. No. US 1991-783518, filed on 28 Oct 1991, now abandoned which is a continuation-in-part of Ser.

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PRAI SU 1987-4352833 19871230

DT Utility

FS Granted

EXNAM Primary Examiner: Feisee, Lila; Assistant Examiner: Ungar, Susan

CLMN Number of Claims: 12

ECL Exemplary Claim: 1

DRWN 16 Drawing Figure(s); 8 Drawing Page(s)

LN.CNT 8309

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides methods for normalizing the numbers of lymphocytes in animals by administering the dipeptide L-Glu-L-Trp.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . useful inlcude e.g., Chlorambucil, Cyclophosphamide, Ifosfamide, Mechlorethamine Hydrochloride, Melphalan, Thiotepa, Busulfan, Procarbazine Hydrochloride, Carmustine, Lomustine, Streptozocin, Cisplatin, Carboplatin, Dacarbazine, Altretamine, **Mesna**, Methotrexate, Leucovorin Calcium, Cytarabine, Floxuridine, Fluorouracil, Cladribine, Fludarabine, Mercaptopurine, Pentostatin, Thioguanine, Hydroxyurea, Bleomycin Sulfate, Dactinomycin, Daunorubicin Hydrochloride, Doxorubicin Hydrochloride, Idarubicin. . . Hydroxyprogesterone Caproate, Medroxyprogesterone Acetate, Megestrol Acetate, Aminoglutethlmide, Mitotane, Aldesleukin, Interferon-.alpha..sub.2a, BCG, Isotretinoin, Levamisole, Octreotide Acetate, Cyclophosphamide, Ifosfamide, Mechlorethamine Hydrochloride, Melphalan, **Mesna**, Busulfan, Carmustine, Lomustine, Nimustine, Semustine, Streptozocin, Cisplatin, Carboplatin, Iproplatin, Procarbazine Hydrochloride, Dacarbazine, Altretamine, Sodium Phosphate P.sup.32, Chromic Phosphate P.sup.32, Methotrexate,. . .

DETD . . . patients with thoracic cavity tumors and other cancers after radiation therapy (EXAMPLE 3, Protocols A-C, below); ii) patients having occupational **radiation exposure** (EXAMPLE 12, Protocols A and B); and, iii) patients following adult thymectomy (EXAMPLE 24). Illustrative examples of other immunocompromised patients. . .

DETD . . . World J. Surgery 16 (5): 918-923). Hematological data have also been used to construct an empirical dose curve for gamma **radiation exposure** at Chernobyl and values reported for 127 of the former residents range from 0.5 Gy to 12 Gy (Konchalovskii, M.. . .

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Examination Group			
Healthy			
Laboratory Indicia.sup.a	Normal Controls	Accidental **Radiation Exposure** Before	After Thymalin

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Treatment of Radiation-Induced Immunodeficiency:
Treatments with Thymalin at Two Months Post-**Radiation Exposure** (X .+-.
m)

Examination Group	Healthy	Accidental Irradiation	
Indicia.sup.a	Normal Control		
		Before	
			After Thymalin Treatment
Leukocytes, abs	5.6 .+-. 0.8	3.5 .+-. 0.4*	

. . .
DETD . . . occur in subjects exposed to radiation, presumably because of decreased immune surveillance and elimination of tumor cells. At three years post-**radiation exposure,** preliminary evaluation of patients exposed to radiation at Chernobyl suggested lingering impaired immunity in 20% of the subjects as evidenced. . .
DETD TABLE 6

Indices of Cellular Immunity and
Innate Immunity in Chernobyl Subject Receiving
Treatment with L--Glu--L--Trp at 3 Years Post-**Radiation Exposure**

	Laboratory Test Results		
	Before	After	
Indicia	Therapy	Untreated	L--Glu--L--Trp
Leukocytes, abs	5.8 .+-. 0.3	5.5 .+-. 1.0	5.6 .+-. 0.4
Lymphocytes, abs	2.0. . .		

DETD Occupational **Radiation Exposure**
DETD . . . in anti-bacterial, anti-viral, and anti-parasitic immunity. The levels of lymphocytes in thymus, spleen, and lymph node are decreased following sub-lethal **radiation exposure,** and the effects of L-Glu-L-Trp on recovery of immune function following **radiation exposure** were investigated in this model. 142 guinea pigs were exposed to 1 Gy of X-irradiation and then treated with L-Glu-L-Trp. . .

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